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DEPARTMENT OF THE AIR FORCE

AIR UNIVERSITY

AIR FORCE INSTITUTE OF TECHNOLOGY

Wright-Patterson Air Force Base, Ohio

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AFIT/GSO/ENG/90D-2

AN ANALYSIS OF THE EFFECTS OF PHENYTOIN
IN TREATING MOTION SICKNESS AND THE
EFFECTS OF MOTION SICKNESS ON THE
HUMAN ELECTROENCEPHALOGRAM

THESIS

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AFIT/GSO/ENG/90D-2

THESIS APPROVAL

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THESIS TITLE: An Analysis of the Effects of Phenytoin in Treating Motion Sickness and the Effects of Motion Sickness on the Human Electroencephalogram

DEFENSE DATE: 21 November 1990

GRADE:

COMMITTEE:	NAME/DEPARTMENT	SIGNATURE
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AN ANALYSIS OF THE EFFECTS OF PHENYTOIN IN TREATING

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THESIS

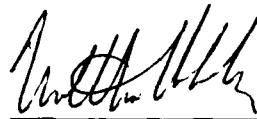Presented to the Faculty of the School of Engineering

of the Air Force Institute of Technology

Air University

In Partial Fulfillment of the

Requirements for the Degree of

Master of Science in Space Operations

Todd M. Banducci, B.S.

Captain, USAF

December 1990

Preface

This research furthered AFIT's investigation of the therapeutic efficacy of the anticonvulsant drug phenytoin in preventing or delaying the onset of motion sickness. In addition, new equipment was used to construct color topographical maps of the subjects' recorded EEG signals which were analyzed to determine if a point of origin and/or a propagation pattern for motion sickness could be discerned.

I thank Dr. Matthew Kabrisky, my advisor, for his unending patience, insight, encouragement, faith, and assistance. I will always be grateful for his ability to calm and reassure me. I thank Dr. William E. Chelen for his guidance and assistance. His knowledge, skills, and expertise as both a physician and an electrical engineer were invaluable. I thank Majors Thomas S. Kelso and Steven K. Rogers for their much needed feedback on this thesis. I thank Capt Nagin Ahmed for her help during the experimental trials and Mr. Barry J. Boettcher for his friendship and help in the library. I thank Mr. Charles M. Powers, Jr., for procuring supplies and equipment and providing facility support.

I would also like to thank my wife, Babette Renee, and my son, Paul Michael, for their love and support, without which I'd have never made it. And finally, I'd like to thank my God who made this all possible.

Todd Michael Banducci

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Abstract

This research had two goals: to continue the ongoing research at AFIT to determine the efficacy of the anticonvulsant drug phenytoin in combating the onset and progression of motion sickness; and to note whether or not there is a discernable similarity in the brains of the test subjects to indicate a common point of origin (epicenter) and propagation pattern of the effects of motion sickness in the brain. Eight male DoD personnel were used as subjects to complete twelve trials. Four subjects completed the phenytoin verses placebo double-blind crossover experiment. These four subjects experienced a 99% mean increase in their times-to-emesis and a 613% mean increase in their symptom-free-times, with one subject remaining asymptomatic throughout his phenytoin trial. Although some general tendencies were noted, no clearly evident point of origination or propagation pattern for motion sickness could be discerned in the brain.

AN ANALYSIS OF THE EFFECTS OF PHENYTOIN IN TREATING MOTION SICKNESS AND THE EFFECTS OF MOTION SICKNESS ON THE HUMAN ELECTROENCEPHALOGRAM

I. Introduction

Background and Justification

Is motion sickness a problem? Do experienced aviators and astronauts get sick? The answer to both of these questions is yes. Have you ever read the label on a motion sickness bag? It states the following:

> For use during moments of stomach upset. If an upset stomach is anticipated, remove bag from this container and keep ready for use. Do not be embarrassed by this precaution as even veteran travelers are subject to occasional motion sickness. (8:51)

As the label indicates even veteran travelers are susceptible to motion sickness and one example of what compounds the problem today is that many of the astronauts on current shuttle missions, such as mission specialists, are not veteran travelers and may be even more susceptible to becoming sick.

Motion sickness is a serious problem facing the Department of Defense. It is a major cause of elimination of pilot candidates in Undergraduate Pilot Training (UPT)

with up to 40% of the student pilots experiencing some form of airsickness (36:1152). In FY89, there were 1,931 UPT students. Of the 1,931 students, 477 were eliminated for various reasons. Thirty-six of these students were required by Air Training Command (ATC) to discontinue their training because they suffered from acute airsickness. Statistics are not available on the number of students who left UPT under other reason codes (Self Initiated Elimination (SIE), for example) as a direct result of or at least influenced by their suffering airsickness. It is not unreasonable to expect that the number was significant (45). Motion sickness can greatly affect even veteran fliers and can occur during high-g maneuvers, low level missions, and even while in a simulator. For backseaters and flight crew (navigator, crew chief, etc.), a "normal" flight in choppy air may be sufficient to induce motion sickness (17:470-473; 36:1152; 41:10).

Motion sickness in space (or Space Adaptation Syndrome) established itself as a major concern beginning with the Apollo program. Space adaptation syndrome symptoms were first reported during Apollo 7. The first real impact occurred on the Apollo 8 mission to the moon in 1968 when mission commander Frank Borman got sick during the outward leg of the trip. Russell Schweickart, who became sick during the Apollo 9 mission, spent four to five years

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working with researchers studying the problem of space motion sickness. During this time, he was subjected to a rotating chair, induced nystagmus, and parabolic flights and was found to be relatively resistant to getting sick, yet he did get space sick and as he put it, getting sick in space "wasn't the right stuff." In total, 10 of the 21 astronauts used in the Apollo program, all of whom were veteran flyers, experienced some form of space sickness. The actual number of affected personnel and nature of the symptoms by mission is shown in Table 1 (8:52-53; 15:1185; 48:6-7).

The problem still persists today with 2 out of every 3 shuttle astronauts getting space sick during a mission. A "Space Motion Sickness Grading Criteria" was developed at the Johnson Space Center in order to record the level of sickness experienced as well as the raw number of astronauts affected (see Table 2 on page 5). Using this criteria, over 50% of the shuttle astronauts have experienced moderate or severe cases of space motion sickness (15:1185-1186). At least two shuttle mission schedules have been significantly impacted because the crew suffered from space motion sickness. The third day's schedule on the third shuttle flight had to be pushed back because both crew members were sick. Schedules were again disrupted during the Spacelab flight in December of 1983. During this flight, medical personnel who had been sent along to conduct tests and

**Table 1 Episodes of Space Sickness
Among Apollo Astronauts (48:7)**

Mission	Nature of Symptoms
Apollo 7	Mild sensations of tumbling (1)*
Apollo 8	Stomach awareness, nausea and vomiting (3)
Apollo 9	Strong sensation of tumbling, anorexia, queasiness (2); persistent nausea and vomiting (1)
Apollo 10	Stomach awareness, anorexia, nausea (1)
Apollo 11	Mild anorexia (1)
Apollo 12	No reported symptoms
Apollo 13	Stomach awareness (2); nausea and vomiting (1)
Apollo 14	No reported symptoms

* number of crew members

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Table 2   Space Motion Sickness Grading Criteria (15:1186)

SPACE MOTION SICKNESS
GRADING CRITERIA

<u>None</u>(0): No signs or symptoms reported with the exception of mild transient headache or mild decreased appetite.

<u>Mild</u>(1): One to several symptoms of a mild nature; may be transient and only brought on as the result of head movements; no operational impact; may include single episode of retching or vomiting; all symptoms resolved in 36-48 hours.

<u>Moderate</u>(2): Several symptoms of a relatively persistent nature which may wax and wane; loss of appetite; general malaise, lethargy and epigastric discomfort may be most dominant symptoms; includes no more than two episodes of vomiting; minimal operational impact; all symptoms resolved in 72 hours.

<u>Severe</u>(3): Several symptoms of a relatively persistent nature that may wax and wane; in addition to loss of appetite and stomach discomfort, malaise and/or lethargy are pronounced; strong desire not to move head; includes more than two episodes of vomiting; significant performance decrement may be apparent; symptoms may persist beyond 72 hours.

gather information in the fight against space adaptation syndrome, experimented on crew members who were already suffering from space sickness symptoms. This testing caused the crew to get quite sick and disrupted their already tight schedule (37:30).

Typically, space sickness assails an astronaut within 24 hours of lift-off. The onset of the sickness can even occur within the first hour with symptoms usually disappearing after three days. It is for this reason that space sickness "has been called the most clinically significant medical phenomenon during the first several days of spaceflight." It is also for this reason that Minimum Duration Flights (MDFs) last at least three days to ensure all crew members have recovered and are ready to perform all entry and landing activities (15:1185; 29:773). The Soviet Union has what appears to be a great advantage over the United States due to the luxury of time. Because of the extended length of most Soviet missions, their cosmonauts are allowed to slowdown for a few days to adjust to the weightlessness if they are feeling ill. The United States cannot do this as shuttle missions are far too short, too costly, and too hectic to accommodate this sort of slowdown. For example, it would often be totally unacceptable to delay or reschedule the deployment of a satellite, be it of national

military importance or of a paying customer, due to crew illness (8:51-52).

Another problem presented by space sickness is that of crew safety during an extra vehicular activity (EVA) such as a spacewalk. An EVA is a very complex and dangerous maneuver that requires the total concentration of those involved. Any level of space sickness can distract the astronaut and increase the odds of a tragedy. Asphyxiation may even occur should an astronaut vomit inside a space suit, the same way a pilot could asphyxiate if he got sick while wearing his oxygen mask. Emesis in space can occur very suddenly, therefore those astronauts demonstrating even the slightest symptoms of space sickness are prohibited from participating in an EVA and none are scheduled during the first three days of flight. EVA's were cancelled due to sick crew members on both Apollo 9 and STS-5. It would not be a good situation if an entire crew became sick and an EVA needed to be performed as there is no contingency plan at this time (15:1185; 53:3-4).

The National Aeronautics and Space Administration (NASA) has said that the impact of space motion sickness is so significant that it costs them about $10 million per mission (9; 40; 47:A3).

Motion Sickness Defined (Symptoms)

Motion sickness is defined by the American Heritage Dictionary as:

> A malady induced by motion, as in travel by
> airplane, car, ship, or other vehicle, and charac-
> terized by nausea, vomiting, and often dizziness
> (1:856).

The American Heritage Dictionary goes on to define space

sickness as:

> Any of various ailments resulting from manned space
> flight, such as nausea resulting from prolonged
> weightlessness (1:1237).

As defined above and understood in practice, space

adaptation syndrome, or space sickness, is a form of motion

sickness. For the purpose of this paper, the three

different names will be considered synonymous and

interchangeable.

A person (be it pilot, astronaut, or fisherman) who is a

victim of motion sickness will usually have experienced very

common and predictable symptoms. The symptoms are charac-

terized by the following physiological conditions:

1) the victim often breaks out in a cold sweat;

2) the victim may begin to salivate and swallow

repeatedly;

3) gastric awareness (stomach nausea/stomachache)

usually occurs;

4) the individual can become quite pale and sickly

looking;

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5) and finally, when the individual's own unique
tolerance level has been exceeded and the point of
emesis has been reached, the victim vomits, often
repeatedly.

Other symptoms that may be encountered between the onset of
the condition to the point of emesis include drowsiness,
dizziness, lethargy, loss of appetite, fatigue, warmth,
coldness, headache, anxiety, dry or acid mouth, tingling, a
spinning sensation, lightheadedness, hyperventilation,
belching or flatulence, and disorientation (8:52; 17:469-
470; 37:30).

Motion sickness can therefore be described as a type of
sickness (malady) encompassing air, sea, land (car, armored
personnel carrier, etc.), space and any other form of
sickness induced by perceived or actual motion wherein there
is a change in an organism's homeostasis typically
characterized by nausea, dizziness, pallor, cold sweating,
and vomiting resulting from a sensory conflict within the
brain (17:468; 41:10; 53:2; 66:1).

Motion Sickness Cause

The currently accepted explanation as to the cause of
space adaptation syndrome is the Sensory Conflict Theory,
which results from a perceived error in the continuous data
received by the brain from the visual system (eyes) and/or

the vestibular system (inner ear) on the position and movement of the body (8:52-53; 17:474; 53:2; 59:25-26). There are two kinds of sensory conflict (derangement) that cause motion sickness. The first is inter-modality conflict which is between the eyes and the inner ear (17:477-478; 48:5; 59:26). One example of this type of conflict occurs when an airline passenger focuses on a wall (or object) before him, devoid of any external visual reference. The eyes report a lack of apparent motion to the brain as the passenger moves in concert with the wall. But, if the plane is pitching or bouncing due to turbulence, the inner ear will be sending messages to the brain, reporting numerous sharp motions. The messages received by the brain conflict and this disparity may result in the passenger becoming sick (64:2). A second example occurred during a shuttle mission when a crew member, after noticing the earth at a peculiar angle out of a window, vomited suddenly and without warning (8:54). The earth looked "funny" and its appearance was not as expected based on previous information received by the brain.

The second type of conflict is intra-modality conflict (or intra-labyrinthine conflict) and involves only the inner ear. The two areas of conflict within the inner ear are the semicircular canals and the otolith organs (17:477-479; 48:5; 59:26). To better realize why these two areas have

such a profound effect, it is necessary to understand how

they work. The following quote explains this in detail (See

Figures 1 and 2, pages 12 and 13):

> The inner ear's vestibular cavity is the point of
> entry for the signals that tell us where we are and
> how we move. Linear motion and the constant force
> of gravity are sensed by the inner ear's otolith
> ("ear stone") organs, which contain calcite crystals
> that lie like a carpet on a sensory membrane in the
> labyrinth of the inner ear. If you sit motionless,
> the otolith registers gravity alone; linear movement
> (forward, backward or up and down) and acceleration
> cause the crystals to shift and move the hair cells
> on which they sit. These send signals to the
> cerebellum and brain stem, which perform the complex
> job of making sense of these signals.
>
> Another element of our internal guidance system
> consists of three tubes in the inner ear called the
> semicircular canals. These narrow pipes contain
> fluid that moves through the canals when you rotate
> your head, and signals rotational or angular
> movement. (37:32)

Motion sickness from this form of conflict is produced by

stimulation of the semicircular canals with cross-coupled

angular accelerations while the position of the head is

moved out of the axis of rotation. Figures 3 and 4 on page

14 depict how this required cross-coupling can occur. The

result is the production of the Coriolis Effect. The

Coriolis Effect results in a perceived motion and whole body

rotation about an axis that is orthogonal to both the tilt

position of the head and the rotational axis of the body.

An example would be when a pilot, either accidentally or by

necessity, quickly moves his head during a high-g maneuver.

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IT'S IN YOUR EAR—YOUR INNER EAR

The inner ear's vestibular cavity is the point of entry for the signals that tell us where we are and how we move. Linear motion and the constant force of gravity are sensed by the inner ear's otolith ("ear stone") organs, which contain calcite crystals that lie like a carpet on a sensory membrane in the labyrinth of the inner ear. If you sit motionless, the otolith registers gravity alone; linear movement (forward, backward or up and down) and acceleration cause the crystals to shift and move the hair cells on which they sit. These send signals to the cerebelium and brain stem, which perform the complex job of making sense of these signals.

Another element of our internal guidance system consists of three tubes in the inner ear called the semicircular canals. These narrow pipes contain fluid that moves through the canals when you rotate your head, and signals rotational or angular movement.   —C. J.

INNER EAR

Semicircular Canal

Gelatinous Membrane

Ear Stones

Hair Cells

Otolith Organs

Vestibular Cavity

Figure 1   The Inner Ear (37:32)

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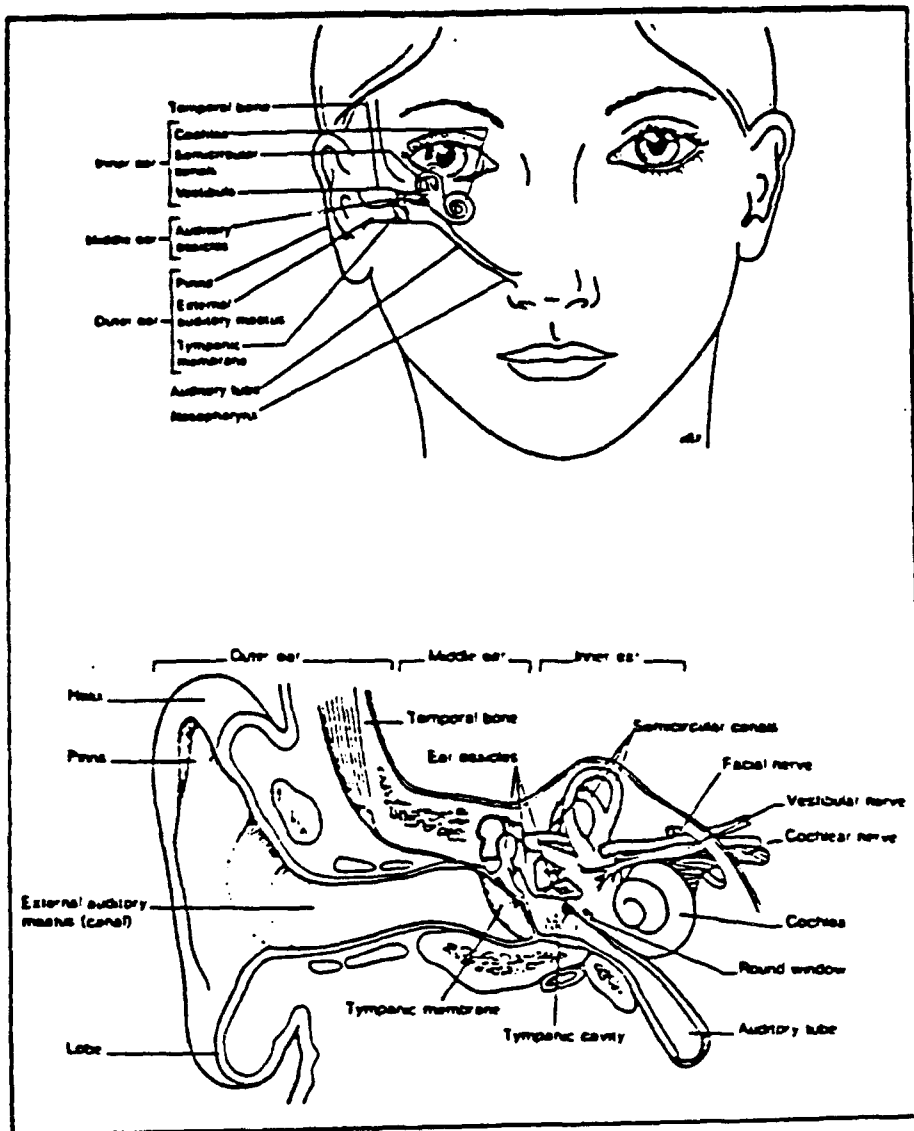
Figure 2 The Vestibular Cavity (48:3)

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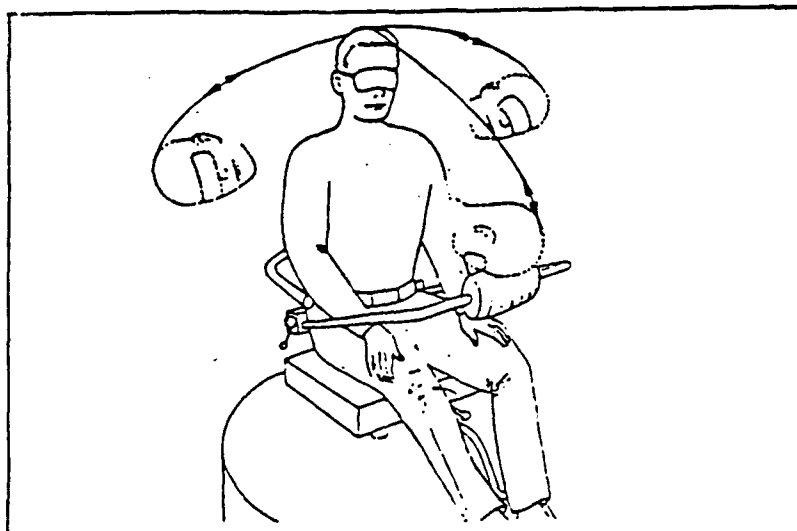
**Figure 3 Schematic Illustration of Rotating Chair
Used to Induce Motion Sickness Response (51:602)**
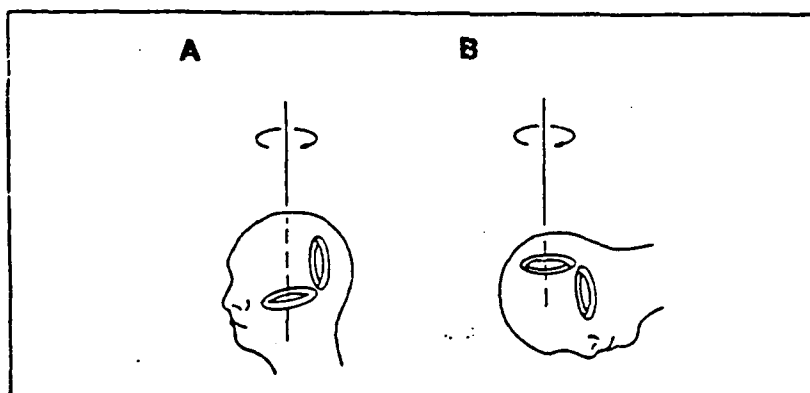
**Figure 4 Schematic Illustration of Cross-Coupling
(42:230)**

If an individual rotates clockwise at a constant velocity
and tilts his head forward 90 degrees, his horizontal semi-
circular canal will signal counter-clockwise velocity and
his vertical semicircular canal will indicate clockwise
velocity.

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The angle of head tilt, direction of head movement, and speed of rotation are all contributing factors which determine the magnitude and persistence of the motion sickness experienced by an individual (48:2; 50:9; 59:49).

Space adds a bit of a twist to the equation for motion sickness. Space adaptation syndrome can occur for a reason unique to weightless environments. What occurs is still a conflict within the inner ear, but for a different reason. Just as on earth, the fluid within an astronaut's semicircular canals has inertia, signaling rotational or angular movement. However, the gravity which acted upon the otolith organs is no longer present. Thus a force acting on the calcium carbonate crystals and recognized as normal by the brain is absent. This results in abnormal signals being sent to the brain from the otolith organs while the semicircular canals are still sending normal, business-as-usual, signals. This mix of signals combines to produce a form of intra-modality conflict peculiar to weightless conditions such as during manned space flight (2:319-321, 324-325; 8:53).

Two types of conflict have been discussed, inter-modality and intra-modality. At the Air Force Institute of Technology the work has centered around intra-modality conflict. This has been accomplished through a standardized routine of experimentation which effectively eliminates the

occurrence of inter-modality conflict through the use of a blindfold. All test subjects are blindfolded to prevent the eyes from sending visual signals to the brain. The Coriolis Effect (intra-modality conflict) is induced through the use of systematic head movements, again as depicted in Figures 3 and 4. These movements begin a few minutes after the chair has begun spinning, occurring every 10 seconds. At 10 second intervals, the head is moved its full range-of-motion; either up, down, right, or left. This succession of head movements, plus the rotation of the chair have proven to be more than adequate in developing the Coriolis Effect in test subjects.

Problem Statement

Primary Objectives.

The proposed research will have two related, yet clearly distinct, primary objectives which were chosen due to their ability to be investigated coincident to one another. The objectives are as follows:

1. To note whether or not there is a discernable similarity in the brains of the test subjects to indicate a common point of origin (epicenter) and propagation pattern of the effects of motion sickness in the brain;

2. To continue the ongoing research to determine the

efficacy of the anticonvulsant drug phenytoin in combating the onset and progression of motion sickness.
Sub-objectives.

Due to the nature of the research and the fact that the two objectives will be pursued simultaneously, the basic sub-objectives will be the same for both. They are as follows:

1. Determine what test procedures will be employed to reach the primary objectives;

2. Obtain permission to use human subjects (DoD personnel-active duty, male) in the experimentation;

3. Identify test subjects that can be safely used for these experiments;

4. Test and validate the equipment to ensure that it meets requirements and is compatible with the human subjects;

5. Conduct the experiments;

6. Collect data as the experiments proceed;

7. Analyze the data;

8. Summarize and report the results in a logical, coherent manner.

Scope

This research continued the AFIT motion sickness studies and was limited to the following:

1. Collecting data on physiological functions of subjects up to 5 Oct 90. There were 8 subjects observed.

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All subjects were male military personnel. Females were not accepted as subjects since phenytoin is teratogenic and may affect potential pregnancies.

2. Analyzing the effect of motion sickness on the human electroencephalogram.

3. Analyzing the effect of phenytoin on motion sickness.

Assumptions

The following assumptions were made during this research:

1. Motion sickness has a neurological basis. The cause of its appearance is consistent with the Sensory Conflict Theory.

2. The physiological symptoms accompanying motion sickness resemble those of a partial seizure and can therefore be suppressed, precluded, or possibly even cured by using an anticonvulsant drug such as phenytoin.

3. Motion sickness induced through the use of a rotating chair and systematic head motions is similar to that observed in the real world.

4. Distinct and measurable changes in physiological parameters occur during the evolution of motion sickness and these changes can be correlated to the level of motion sickness experienced and reported by the subject. Thereby, physiological parameters can be used to predict motion sickness levels.

5. All observed physiological changes were in fact a result of motion sickness and not sensor or measuring equipment malfunctions or anomalies.

6. Subjects were accurate when self-reporting motion sickness levels despite the subjective nature of these self-appraisals (5:773, 776).

7. There is a change in a subject's EEG signals during the onset and progression of motion sickness from his normal, at rest, eyes closed condition (10; 13:1023-1024).

8. No adaptation occurs from trial to trial -- subject is equally susceptible for each trial (68:556, 568-572).

9. Subjects are in good health and any abnormality or illness of the vestibular systems would be detected.

10. Results obtained from subjects are typical and characteristic of each subject and the population at large.

11. The same results would be attained if a subject repeated the experiment over and over. Therefore, the experiments are reproducible.

Equipment, Facilities, and Materials

Equipment.

The following equipment was used during the course of this research.

1. A Neurokinetics Model 8010 rotary chair system - an electrically powered rotating chair (equipped with

a safety belt), used to elicit the motion sickness response.

2. A chair speed, direction, and attitude control console (includes a 386 personal computer system and a chair control panel).

3. 14 platinum subdermal EEG electrodes and accompanying channels for measuring brain wave activity.

4. A Marshall Electronics Astropulse 90 Blood Pressure Cuff (sphygmomanometer) to measure arterial blood pressure.

5. Two circumferential belts (pneumographs) that employ strain gauges to detect respiration rate and depth changes for measuring both abdominal and thoracic respiration.

6. Two thermistors for measuring skin temperature.

7. Two galvanic skin response (GSR) electrodes for measuring skin conductance.

8. Two plethysmographs (photo transistors, resistors, and an LED mounted in an epoxy housing) for measuring blood flow volume (skin pallor). They are self-adhesive with one mounted on the subject's cheek and the other on the index finger.

9. A phonosplanchnograph (an Intech Systems Corporation Dif-Stet differential stethoscope) to

record audible gastrointestinal mechanical activity.

10. Two electrosplanchnographs to record electrical gastrointestinal activity.

11. Two electronystagmographs to measure horizontal and vertical eye movement (blinking).

12. An electrocardiograph to measure heart rate.

13. A ballistocardiograph to measure heartbeat strength.

14. An Ace elastic bandage and manual blood pressure cuff for pallor calibration.

15. A Spirometrics Flowmate Model 2500 clinical spirometer.

16. A Puritan-Bennett/Datex Instruments Corporation model 223 Expired Carbon Dioxide Monitor.

17. A Panasonic Audio-Visual System:

    a. A video cassette recorder to record trials;

    b. Two cameras, one mounted on the rotating chair and one mounted on a tripod;

    c. A 19" video monitor;

    d. A control panel;

    e. Two microphones, one mounted on the rotating chair (next to the camera) and the other mounted on the rotating chair control console;

    f. An audio mixer.

18. An INTECH Systems Corporation Micro-Tracer (portable, battery operated 12-lead EKG).

19. A Fluke Model 8022A Multimeter

20. A Delmar Avionics Model 501 EEG/ECG Calibrator/Tester.

21. A SOLTEC Corporation Model 8K26-1-L 16-channel strip chart recorder (pen oscillograph).

22. Two Kyowa Dengyo Electronic Instruments Company RTP-610AM 14-channel Beta tape recorders.

23. A Zenith 248 personal computer for real-time data display (using CODAS Software) and analysis (using ASYSTANT Software) and a Zenith 248 for word processing.

24. A Hewlett-Packard LaserJet Series II printer.

25. A Bio-logic 248 personal computer system including Brain Atlas software (with brain mapper) and a Model PJ-1080A color printer.

26. A Cyborg Corporation Thermal P642 digital thermometer to measure ambient air temperature in the laboratory during trials.

27. An AMPEX 60 minute audio cassette tape with recorded head movement commands.

28. An Audio Visual Systems Incorporated Model 2873 portable cassette tape player which played the recorded head movement commands.

29. A Commodore 64 personal computer system and a Star Gemini-10x printer used to perform and record cognition and performance tests to establish a baseline score and prior to trials.

30. A Ritter Medical Products Model M7 Speed Clave used for sterilization of subdermal platinum electrodes.

31. A Patton Electric Company Incorporated Designer Series Model G-1286 Electric Fan.

Facilities.

The motion sickness experimentation laboratory occupies the front half of Room 242 in the Air Force Institute of Technology's School of Engineering, Building 640. The other facility that was utilized was the laboratory at the base medical center for conducting subject blood tests.

Materials.

The following materials were used during the course of this research:

1. The drug phenytoin (Dilantin);

2. Standard issue Air Force flight sickness bags;

3. Alcohol pads used to clean subjects' skin and scalp before electrode placement or insertion;

4. 3M Durapore Surgical Tape;

5. A standard eye test chart;

6. Two Power Sonic Model PS-1265 12 volt batteries;

7. Electrodes to provide body-to-sensor contact:

(a) Andover Medical Incorporated Medtronic "Huggables" Infant Montoring Electrodes (electronystagmograph);

(b) 3M "Red Dot" Monitoring Electrodes (electronystagmograph);

(c) NDM Corporation Silvon (silver/silver chloride) Stress Test ECG Electrodes (electrocardiograph and electrosplanchnograph);

(d) CONMED Corporation Adult ECG Electrodes (silver/silver chloride) (electrocardiograph and electrosplanchnograph).

8. JVC T-120 video cassette tapes;

9. 5 1/4" floppy disks (DS, HD).

10. Beta video tapes used in the 14-channel Kyowa Beta tape recorders;

11. Subject medical history and prior motion sickness experience questionnaires;

12. Subject consent forms;

13. Software used for analysis, data processing, and word processing:

(a) WordPerfect 5.0, by Wordperfect Corporation;

(b) WordPerfect 5.1, by Wordperfect Corporation;

(c) DOS 3.31, by Microsoft Corporation;

(d) DOS 4.01, by Microsoft Corporation;

(f) DESQview 2.25, by Quaterdeck Office Systems;

(g) ASYSTANT 1.10, by Asyst Software Technologies, Inc., MacMillan Software Company;

(h) CODAS, by Dataq Instruments, Inc.;

(i) QUATTRO, by Borland;

(j) STATISTIX, by NH Analytical Software;

(k) and Harvard Graphics 2.10, by Software Publishing Corporation.

Principal Technical Support

Dr. William E. Chelen (M.D., B.S.E.E.) was the backbone of this research. He provided the critical corporate knowledge of the motion sickness research conducted at AFIT since 1985. He acted as chief, and probably more precise, sole technician having designed and constructed a majority of the physiological sensors being used to include the very uniquely sensitive extended-frequency-range EEG amplifiers. He screened and tested all potential subjects. As the resident physician, he was responsible for administering the anticonvulsant drug phenytoin, for conducting pre-trial physical examinations, and for monitoring the physical well-being of all the subjects during and after each experiment. Dr. Chelen also provided invaluable guidance and advice during the course of the research.

II. Experimental Methodology

While all the sub-objectives are common to both main objectives, only part of the methodology was the same. Prior to the methodologies, the sub-objective to which they apply will be denoted in short form. Which main objective they apply to will also be given. Objective 1 will be designated as Brainwaves and Objective 2 as Efficacy.

Determine Test Procedures

(Brainwaves/Efficacy) Appropriately modified test procedures previously used at AFIT.

Permission

(Brainwaves/Efficacy) Permission was requested through the submission of the intended protocol (see Appendix A) to the Human Use Review Committee at the Armstrong Aerospace Medical Research Laboratory (AAMRL). The protocol detailed the experiments to be conducted and how the test subjects would be used.

Identify Subjects

(Brainwaves/Efficacy) The process to identify subjects began when the need for subjects was made known by word of mouth and posted fliers. The prospective subjects who responded were asked to fill out questionnaires (see Appendices B and C) on their medical history and prior

motion sickness experiences and to sign a consent form (see Appendix A). The potential subjects were given a complete physical by Dr. Chelen and were required to have a complete battery of blood tests run by the base medical center. Those with any medical history or current medical condition that indicated the testing could be dangerous for them were immediately rejected. Potential subjects performed tandem Romberg and one-legged balance tests and were subjected to a susceptibility test run in the chair to determine if their vestibular systems were normal. The test run occurred at a rotation speed based on their self-reported susceptibility which was sufficient to produce mild nausea and the onset of motion sickness. The individuals also completed the performance-cognition battery of tests to provide a baseline for future comparison. If a subject had a normal vestibular system, no history of medical problems, and was in good health, he was accepted as a test subject. All test subjects were active duty, male DoD personnel. It is appropriate to note that females were not accepted as test subjects because phenytoin is teratogenic and may affect potential pregnancies.

Test and Validate

(Brainwaves/Efficacy) The EEG electrode system was
tested to ensure the correct registering and transmitting of
brain activity. This was accomplished by having one of the
investigators fitted with the electrodes and subjected to a
test run similar to a susceptibility test run. The
remainder of the testing and validation was accomplished by
a routine operations check prior to the run and fine tuning
(calibration) of the sensors after placement on the subject.

Conduct

(Brainwaves/Efficacy) Each experiment began the day
prior to the trial when the test subject was given two
envelopes marked A and B containing five capsules of either
dextrose placebos or phenytoin. The subject determined from
which envelope to take capsules for each trial (with all
five capsules taken from that envelope for that trial) and
did not reveal which envelope corresponded to which trial
until both trials had been completed. The trials were
spaced at least one week apart and were in opposite
directions (one clockwise, the other counter-clockwise) to
preclude any possible adaptation by the subject that might
otherwise occur if the trials were too close in time to one
another or in the same direction (68:566, 568-572). Only
Dr. Chelen, the resident physician and principal

investigator, knew which type of capsules were in which
envelope. The capsules were taken as follows: one late
that afternoon, one with dinner that evening, one with an
evening snack, one just prior to bed with food, and the last
one was taken the next morning with breakfast. Each active
capsule contained approximately 200-225 milligrams of
phenytoin for a total of about 15 milligrams of phenytoin
per kilogram of the subject's body weight. This protocol
was used to achieve a blood level of approximately 10-20
mcg/ml, which is the normal therapeutic range for phenytoin
(4:1541; 11:1,8; 12:2,5). This procedure for taking the
capsules was repeated for the second trial.

The dosing sequence was altered midway through 1990.
This was in response to a suspicion of the investigators
that some subjects were not getting the full benefit of the
treatment due to the rapid ("acute") phenytoin dosing. This
effect may have been reducing or even eliminating the
efficacy of the phenytoin to combat motion sickness. Those
subjects who realized little or no benefit from the
phenytoin (8 out of 25) had therapeutic blood serum levels,
so a lack of phenytoin in the system was not the problem.
There was, however, a commonality among these subjects in
that certain symptoms/side effects such as a ringing in the
ears (tinnitus) and/or a reduced auditory acuity resulted
from the dosing. These side effects have been shown to

occur in some subjects as a result of acute dosing (13:1023; 46:1141) It does appear that each subject has his own unique tolerance to phenytoin during acute dosing and some are unable to gain benefit from it using acute dosing. For some, it appears the body needs more time to adjust to and utilize the phenytoin and there is some experimental evidence to support this hypothesis. It was decided to extend the dosing period to eliminate any possible lack of effect caused by the dosing procedure. The new dosing schedule was as follows (assumes a Thursday trial): 1 capsule Monday evening, 2 capsules Tuesday, 2 capsules Wednesday (or 3 depending on the size and metabolism rate of the subject), and 1 capsule Thursday morning. This dosing schedule and the amount of the drug taken take into consideration phenytoin's average half-life of about 22 hours (9; 22:19-25; 28:18; 49:301).

The next phase of the procedure began when the subject executed the performance-cognition test battery (U.S. Air Force's standardized "Criterion Task Set") about one hour prior to the trial to record whether any sensory, cognitive, or motor function impairment had occurred due to ingested medication. The subject had previously practiced the battery of tests and a baseline score was established. At this time, Dr. Chelen interviewed the subject to find out if he had experienced any side effects to the medication taken.

Dr. Chelen also administered a brief physical examination to ensure good health prior to the trial. During the exam, he tested the subject's eyes for acuity, range-of-motion, and nystagmus (involuntary eye motion). Once the subject was declared fit to continue, and all pertinent data from the interview had been recorded, he was outfitted with the various physiological monitoring devices and sensors, to include the 14-channel electroencephalogram (EEG) electrodes (see Figures 5 and 6). Prior to the placement of dermal and sub-dermal sensors, all application points were thoroughly scrubbed and cleaned using alcohol pads. The 14 EEG sensors were placed on the following locations: F7, F3, F4, F8, T3, C3, C4, T4, T5, P3, P4, T6, O1, and O2. A blood sample was drawn by a technician from AAMRL, at a convenient point during this phase, to determine his phenytoin serum level.

The subject was then placed in the motion chair. A plastic nose piece with a sampler tube was inserted into the subject's right nostril and taped in place. This was used to measure expired carbon dioxide concentration. Sensors to measure nystagmus, pallor, and respiration were calibrated and tested and the EEG electrodes were tested at this time. The subject's eyelids were taped closed and he was then blindfolded. Thus, the trial began early in the afternoon, almost 24 hours after the subject began taking the capsules. The subject remained sitting at rest to provide about 5

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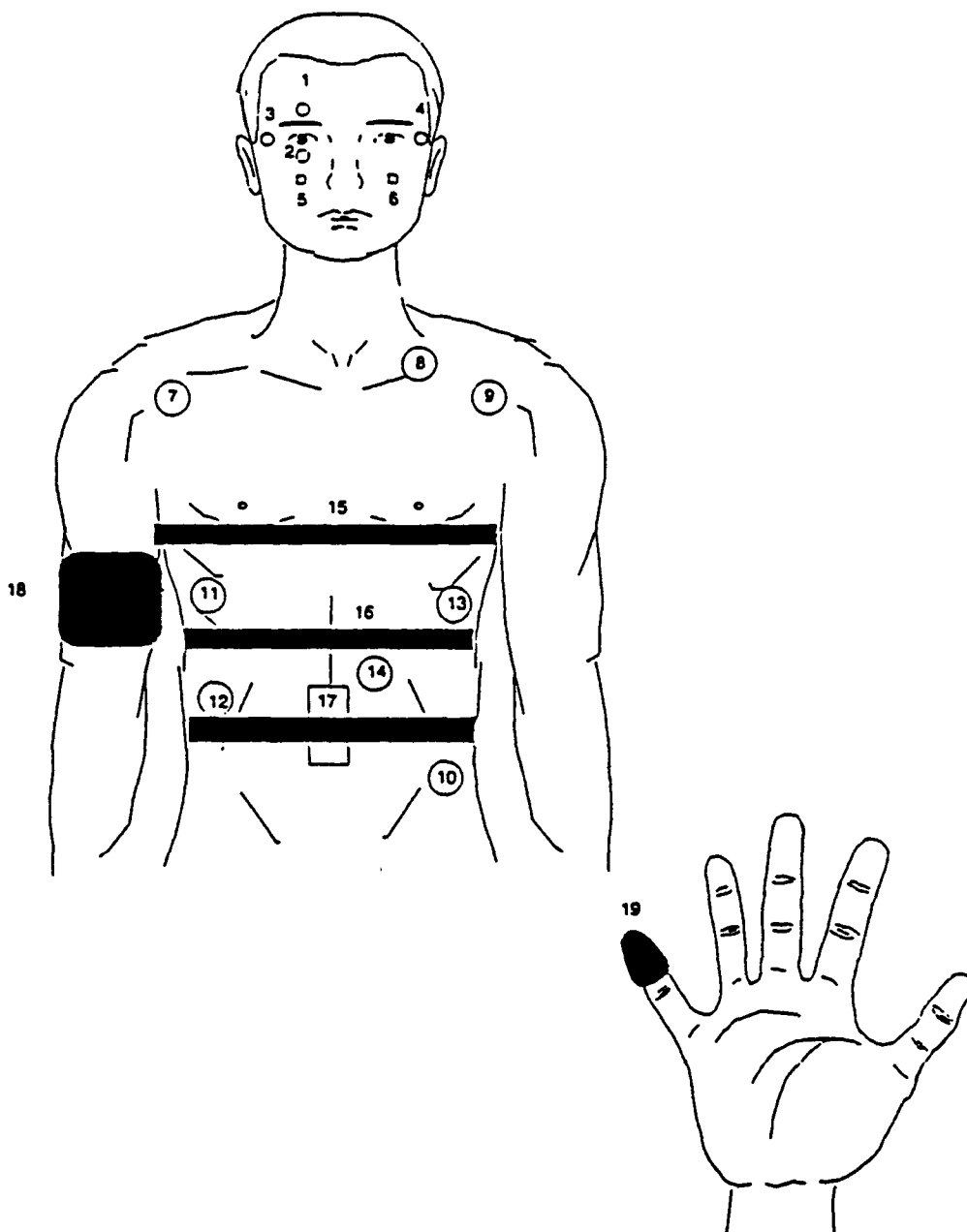
Figure 5 Body Sensor Placement (53:34)
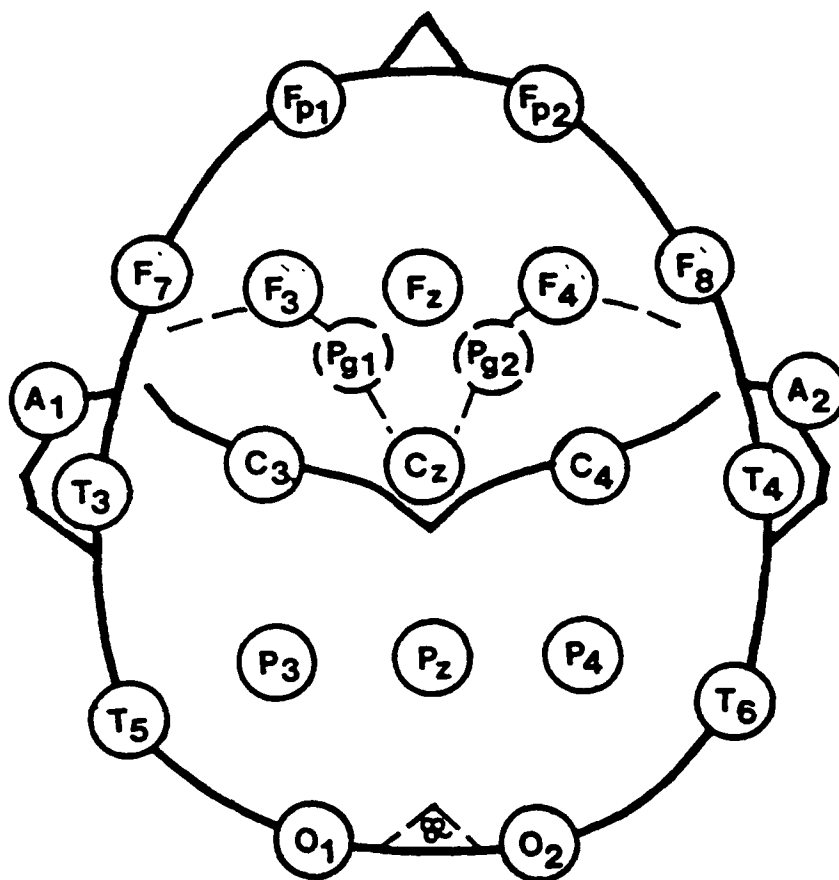
**Figure 6 International 10-20 System Placement
and Letter-Number Designation (60:42)**

Odd numbers on the left, even on the right, and Z or zero
in the midline.

minutes of baseline data. The program for the scheduled rotation speed of the chair was calculated by Dr. Chelen to produce a trial time of about 15 minutes (while on placebo); this was based on the subject's earlier susceptibility test. Rotation, acceleration, and speed were controlled by a computer. The chair slowly accelerated to the scheduled rotation speed. Once the desired speed was reached, a period of about one minute elapsed to allow the subject's vital signs to stabilize and to produce baseline data prior to Coriolis stimulation. An audio cassette tape was then started which verbally directed the subject to perform head movements (up, down, left, and right) every 10 seconds to induce the onset and progression of motion sickness. The subject was constantly monitored by Dr. Chelen and queried as to his subjective condition on a scale of 1 (normal) to 10 (vomiting). He also reported symptoms spontaneously as he experienced them. Notes were taken of the subject's responses and they were also recorded on the VCR tape with the video of the experiment and on the Beta instrumentation tape recording EEG signals. The trial continued until the subject reached emesis (vomited) or was asymptomatic for a maximum of 60 minutes. A subject could also request to terminate the trial at his discretion, but no such requests were made. The chair was then decelerated slowly until it came to a stop and then about 10 minutes of post-run data

was collected while the subject recovered (if necessary). The subject exited the chair and was given a post-run examination. If the post-run exam was satisfactory, which all were, the subject was free to go. (Each person received a t-shirt for participating in the motion sickness studies; this was the sole reward.)

Collect

(Brainwaves) Data were collected by the 14 EEG electrodes as the subject was spinning in the chair (see Figure 6). It was recorded on the Beta instrumentation tape and fed into the Bio-logic computer.

(Efficacy) The data were collected directly by the investigators who annotated the trial start and stop times and any other pertinent information. Information on serum levels was provided by the base medical center based upon their tests of the subjects' collected blood samples.

Analyze

(Brainwaves) The Bio-logic displayed the collected information to be visually analyzed as a series of color brain mappings. The color brain mappings represent the integrated spectral energy over the spatial intervals between sensors. This is accomplished through a paradigm for interpolation in the Bio-logic software. Wave shape

amplitudes were also shown by the Bio-logic system, but these were not used as a basis of analysis.

(Efficacy) The subjects' times versus placebo and phenytoin and versus serum level were plotted out.

Summarize and Report

(Brainwaves) The results are summarized and explained in detail in this thesis through the use of selected mappings at various points (times) in the experimentation.

(Efficacy) The results are summarized and reported in this thesis using a graphical comparison between the times while on placebo and while on phenytoin for the various subjects.

III. Literature Review

Introduction

This section will review the literature pertinent to this thesis research. The discussion covers the three general areas in which scientific research on the study of motion sickness has been done with particular emphasis on the effort being put forth by the National Aeronautics and Space Administration (NASA). It also takes a specific look at the research conducted to date at the Air Force Institute of Technology (AFIT).

The Battle Lines

It is not surprising, based on its impact upon the U.S. space program, that space adaptation syndrome is a major concern of the National Aeronautics and Space Administration (NASA). NASA has many research teams and facilities in its arsenal and is a leader in the fight against space sickness. These include: medical personnel traveling on shuttle flights (8:53), a military version of a Boeing 707 called the "Vomit Comet" whose parabolic flights provide periods of weightlessness of about 25 seconds duration (8:51); Dr. Ashton Graybiel from the Naval Aerospace Medical Institute in Pensacola, Florida (8:53); James Lackner, Graybiel's son-in-law, from Brandeis University (8:53); William Thornton,

an astronaut and physician (8:54); the Massachusetts
Institute of Technology's Man-Vehicle Laboratory (37:32);
Kenneth E. Money, a physiologist with Canada's Defense and
Civil Institute of Environmental Medicine (37:34); NASA's
own Dryden Flight-Research Center in California (37:35);
NASA's Ames Research Center near Palo Alto, California,
where Dr. Patricia Cowings, the "Baroness of Barf," works
with biofeedback (37:36); the Air Force School of Aerospace
Medicine located in San Antonio, Texas, at Brooks AFB
(37:37); and a special laboratory set up at the Johnson
Space Center solely dedicated to the study of space sickness
(37:30-31). There are other individuals and organizations
contributing to the fight, in addition to those listed
above, but they are too numerous to list.

Methods of Attack

The NASA lead attack has been three-fold. Scientific
research is taking place in three areas: drug therapy;
desensitization; and biofeedback, which has received the
most attention.

Drug Therapy.

The first area, drug therapy, has shown limited success
up to this point in arresting motion sickness symptoms. The
major drawback to most drugs currently in use and under
study is that they produce a depressant effect and various

other undesirable side effects which can impair motor skills
and judgement. Because of these side effects, flying
personnel usually do not take any drugs to combat motion
sickness (17:490-492; 64:2-3).

The most successful work with drug therapy through the
mid-80s was done by Dr. Ashton Graybiel from the Naval
Aerospace Medical Institute in Pensacola, Florida. He did
extensive work to validate that a drug, scopolamine,
sometimes worked in preventing or alleviating the symptoms
of motion sickness. Scopolamine had previously (and most
often) been used to treat diarrhea, to calm bowel
hyperactivity, and to treat upper respiratory symptoms.
Scopolamine, as a treatment for motion sickness, had two
major drawbacks. The first drawback was that no one, not
even himself, knew why or how it worked. The second was
that drowsiness was a very common side effect which
scopolamine produced. In order to use the drug on shuttle
astronauts, Dr. Graybiel combined it with dexedrine, a
stimulant, to counter drowsiness. Even with the addition of
dexedrine, shuttle mission commanders were restricted in its
use until orbit was obtained due to their responsibility to
land the shuttle in the event of an aborted lunch. The
combination drug produced mixed results. During the first
five shuttle missions several astronauts took the drug prior
to liftoff, but some still became sick. It appears this

combination is not the answer as yet (4:1691; 8:54; 15:1188; 20:84; 29:773, 776; 57:1, 8; 70:157, 161).

One very positive thing that has come out of Dr. Graybiel's work is his development of a well-defined, easy-to-use diagnostic criteria for grading the severity of motion sickness. His method of grading is the most widely used and accepted today. The diagnostic criteria are illustrated in Table 3. Below, some of the key terms from this criteria are explained.

Terms:

Pathognomonic (Vestibular Sickness): Vomiting, or two major symptoms, or one major and two minor symptoms.

Malaise III: One major, or two minor, or one minor and two other.

Malaise II: One minor and one other, or two minimal, or one minimal and two other.

Malaise I: Any subjective symptom.

Epigastric awareness: a feeling which draws attention to the epigastric area, but is not uncomfortable.

Epigastric discomfort: a feeling of distress which is more that "awareness," but short of nausea. It implies a feeling of being ill.

It must be noted that two symptoms in any of the three lower levels equals one in the higher level. Symptoms are assessed and point values are determined. Sickness level is then defined (29:774; 30:454; 50:8).

Table 3   Diagnostic Categorization of Different Levels of Severity of Acute Motion Sickness (30:454)

DIAGNOSTIC CATEGORIZATION OF DIFFERENT LEVELS OF SEVERITY OF ACUTE MOTION SICKNESS.

Category	Pathognomonic 16 points	Major 8 points	Minor 4 points	Minimal 2 points	AQS* 1 point
Nausea syndrome	Nausea III + retching or vomiting	Nausea II	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		PallorIII	PallorII	Pallor I	Flushing/ subjective warmth≥II
Cold Sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Persistent headache ≥ II
Central Nervous System					Persistent dizziness Eyes closed≥II Eyes open III

Levels of Severity Identified by Total Points Scored

Frank Sickness (FS)	Severe Malaise (M III)	Moderate Malaise A (M II A)	Moderate Malaise B (M II B)	Slight Malaise (M I)
≥16 points	8-15 pts	5-7 pts	3-4 pts	1-2 pts

*AQS--Additional Qualifying symptoms.
+III--severe or marked, II--moderate, I--slight.

Desensitization.

The premise behind this method is that the brain can be taught new "normal" patterns of stimulation. This thinking coincides with the Sensory Conflict Theory in that the brain reacts to abnormal stimuli by inducing sickness; a normal response to an abnormal environment. It was felt that "new" patterns could become accepted by the brain after prolonged and continuous exposure. These "new" patterns would be recognized as normal during flight, thus preventing motion sickness (3:1144; 17:472, 488-489; 68:566, 568-572). NASA's interest in desensitization results from observations of astronauts who become "earth sick." The astronauts' vestibular systems have adapted to weightlessness and this adaptation often persists after landing, sometimes for several days. During this period of readaptation the astronauts are resistant to motion sickness, even when exposed to weightlessness during a parabolic flight in a KC-135. This leads NASA researchers to believe the brain can be "trained" to accept new stimuli as normal (2:325; 15:1188-1189; 37:35; 69:A1, A5). Desensitization is a method that was used extensively on pilots by the British Royal Air Force (RAF) with a 70% success rate from 1973 to 1980. And, with some changes in the program in 1981, they experienced an 84% success rate from 1981 to 1983. The

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method was not as successful as desired and was very hard on the test subjects (3:1147-1148, 1151; 36:1152).

Biofeedback.

The third area of study is in biofeedback. A test subject is hooked up to several monitors and sensors which report such physiological functions as heart rate, skin conductance, depth and rate of respiration, and blood flow to the hands. Using this feedback, test subjects learn how to alter and somewhat control these and other physiological functions. This learned control, along with self-suggestion exercises (autogenic training) and relaxation therapy, helps a person combat and possibly overcome the symptoms of motion sickness. However, biofeedback does not seem to attack the cause (14:399; 36:1153-1154; 64:2-3).

Dr. Patricia Cowings, a psychophysiologist by trade, was the first to try biofeedback on astronauts. NASA gave her six hours, 12 half-hour sessions, to teach astronauts how to control up to twenty of their physiological functions most affected during motion sickness. A subject's progress was tested after every four sessions in a rotating chair with the ultimate goal being to control physiological functions without feedback data and under stressful conditions. Her results have been mixed, but encouraging. One problem with biofeedback that has been identified is that it is necessary to tailor the training differently for each individual

(14:399, 405; 36:1152, 1157; 37:36-37). Dr. David R. Jones led a group of researchers that produced some decent results at the United States Air Force School of Aerospace Medicine. Out of the 53 fliers treated, 45 were able to resume flying with 42 no longer experiencing airsickness. The results were skewed a bit as 10 subjects did not complete treatment (36:1154-1155; 37:37). This method has been fairly successful to date with work in this area continuing.

AFIT Participation

The Genesis.

At this point in time, it is appropriate to discuss how and why AFIT got involved in the battle against motion sickness when so many others are already trying to find a cure. It all began with a letter dated 23 February 1982 from the School of Aerospace Medicine (SAM) at Brooks AFB, Texas, asking AFIT to provide technical assistance in developing a system for the treatment of motion sickness using biofeedback techniques. The system (rotating chair, etc.) was to be capable of collecting up to 16 independent channels of physiological data while inducing the Coriolis Effect on test subjects. SAM also requested that the system and monitoring equipment be computer controlled and require only one technician to operate. The system was to be cost effective, simple to operate, and suitable for use a various

flight training bases (18:I-1 - I-3; 48:14). Thus began AFIT's venture into the world of motion sickness.

1983.

The first AFIT researchers were Captains Earl and Peterson, who worked on the motion sickness problem (with an emphasis on biofeedback) until their graduation in December 1983. They assembled four components which together comprised a Biophysical Data Acquisition System (BDAS). These four components were the rotating chair, a CIM-800 microcomputer, a MASSCOMP MC500 data acquisition computer, and a group of devices for monitoring and measuring the physiological responses of test subjects (18; 24:1-2; 48:14-15). Some of the devices were developed in-house to measure skin pallor, respiration rate, gastric motility, and heart rate. Others were purchased to monitor skin surface temperature and galvanic skin response (18:vii; 48:14-15). They also proposed the development of a subject-dependent mathematical model to accurately predict the progression of motion sickness that would also correlate in time with the progression of motion sickness as reported by the subject (18:I2, V2-V3).

1984.

Next in line to continue the work were Captains Fitzpatrick, Rogers, and Williams. The primary contributions of these men came in two forms -- the

development of a BDAS software that was quite user friendly
and the addition of several new sensors. Two new sensors
for monitoring eye motion and intestinal tone were created
while a thermometer, myograph, and dermograph were purchased
and put in the system (24:vi, 2-3; 48:15).

1985.

The baton was then passed to Captains Jarvis and Uyeda
who became the first to actually collect data on test sub-
jects. They noted several trends in the data. Specifically,
there was an 8% to 20% increase in facial pallor, a 12% to
16% increase in galvanic skin response, and a 600% to 700%
increase in intestinal activity (35:105). Dr. William E.
Chelen, a Clinical Instructor of Aerospace Medicine at
Wright State University and a Professor of Electrical
Engineering at AFIT, also joined the team at this time. He
proceeded to redesign, rebuild, and refine many of the
existing sensors to enhance their performance. He also
designed and built several new sensors to advance the work
(35; 53:15). Dr. Chelen continues today as a permanent
member of the AFIT motion sickness team acting as chief
investigator, physician, and primary tester and designer of
monitoring equipment.

The data collected in 1985 was considered unreliable for
several reasons: environmental conditions were difficult to
control in Building 470 and often varied widely from run to

run and subject to subject; the sample size was too small to be statistically significant; testing procedures were not standardized and consistent; and some of the sensors were suspect, possibly giving invalid information (35:105, 108-110; 48:15).

1986.

The next investigators were Captains Hartle, McPherson and Miller. They moved the chair to Room 150 in Building 640 into what continued as the system configuration (see Figure 7) until December 1989 (48:17). Once there, they relied solely on magnetic tape and strip chart recordings for data collection. They collected data and statistically analyzed it, noting several physiological trends as the subjects approached emesis. The trends were as follows:

1) a 15 to 20 percent increase in pallor;

2) a 10 to 15 percent decrease i. skin temperature;

3) a heart rate increase of 20 to 25 percent;

4) a rate of respiration increase from 20 to 50 percent;

5) a 500 percent change in intestinal noise/activity;

6) a 600 percent change in stomach noise/activity;

7) and up to a 1600 percent increase in amplitude of low frequency brain waves.

However, their data also suffer from a small sample size (12 subjects) and difficulty with environmental control. They
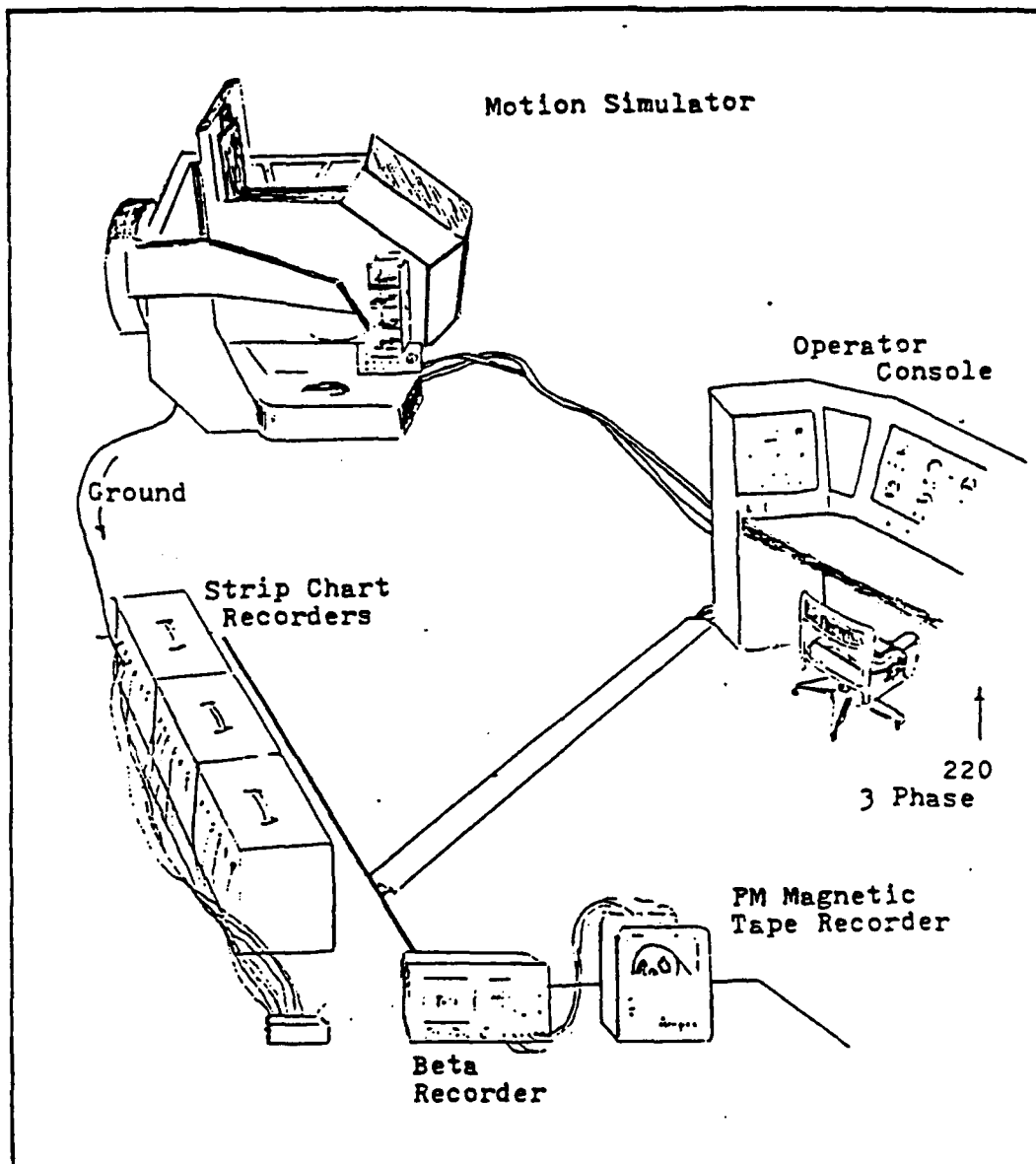
47

Figure 7 System Configuration (48:17)

did begin standardizing test procedures (48:13, 23-28, 64-65; 52:87; 66:18).

1987.

In 1987, Captains Drylie, Fix, and Gaudreault continued the work. A new equation was developed to correlate the level of sickness reported by the subject to the data being recorded by the monitors. Consistent, reliable data were finally collected as procedures were better refined and more standardized and a bank of low pass filters was added to reduce incidental electrical noise. A Zenith 248 Computer was introduced to analyze the experimental data and gastrointestinal noises were monitored for the first time using a differential stethoscope (25:7; 64:4).

1988.

Captains Morales and Scott comprised the 1988 student portion of the team. Their progress did much to advance the work being done at AFIT. They further standardized procedures and collected a substantial amount of valuable data. The still current placement of body sensors and the configuration for EEG sensor placement used through December 1989 were established in 1988 by Captains Morales and Scott. Figures 5 and 8 on pages 32 and 50 illustrate these sensor placements. They also were the first to do any significant work with the drug phenytoin (marketed as Dilantin). As mentioned earlier, the initial emphasis in the work at AFIT
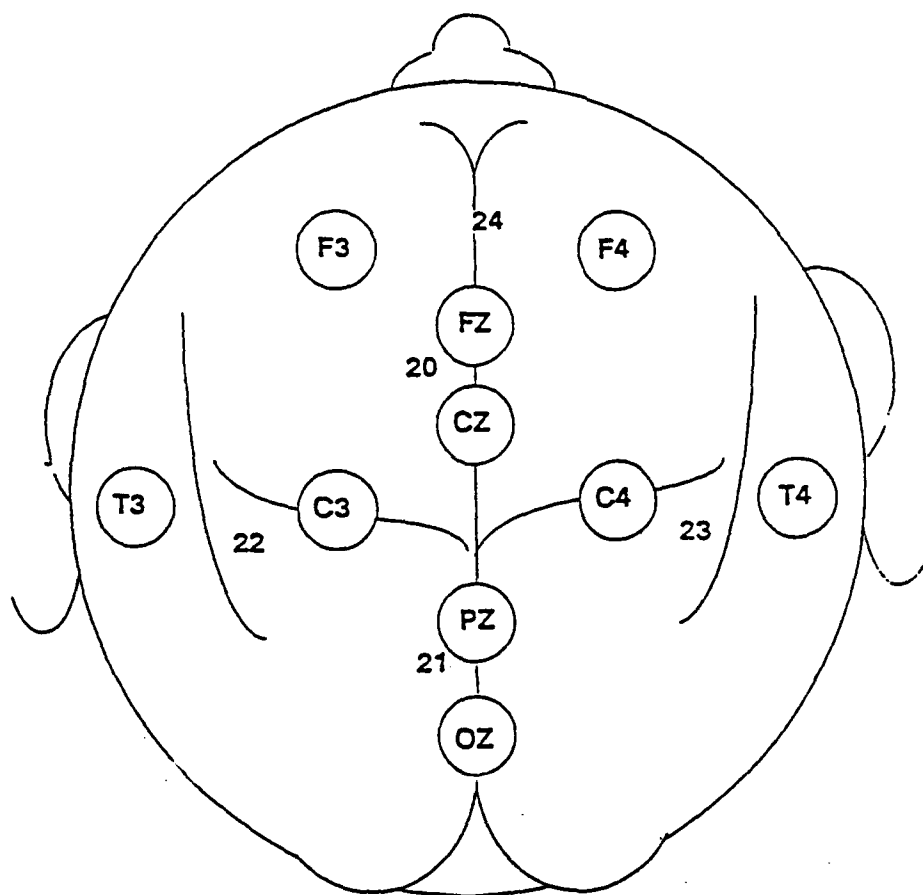
Figure 8   EEG Sensor Placement (53:35)

was on biofeedback. This slowly began to change after a very high amplitude (voltage), very low frequency brain wave(.1 to .2 Hz) was noted after being detected by a special amplifier designed and built by Dr. Chelen (see Figure 9). This unusual brain wave was first detected in 1986 (10:5-8; 48:viii, 53, 56). Dr. Chelen recognized the brain wave to be similar to those that occur during a psychomotor (or partial) epileptic type seizure, but of a much greater magnitude. Dr. Matthew Kabrisky, a Professor of Electrical Engineering at AFIT, who is also the head of the AFIT motion sickness team and had previously worked in an epilepsy clinic, concurred with Dr. Chelen's assessment of the brain wave.   It was also noted that many of the symptoms common to motion sickness, such as epigastric sensation, gastrointestinal hypermotility, cardiovascular and respiratory irregularities, and hyperventilation are also common-place during psychomotor (partial) seizures. Dr. Chelen felt that motion sickness might be treatable using an anticonvulsant drug if it was, in reality, a form of a psychomotor seizure similar to an epileptic seizure (10:9-10; 11:1, 3-4; 13:1022-1024; 20:84, 86; 53:10; 58:449, 452-454).

This new discovery and accompanying theory spawned a whole new approach to studying motion sickness at AFIT. The drug chosen for testing was phenytoin. Phenytoin (5, 5-

51
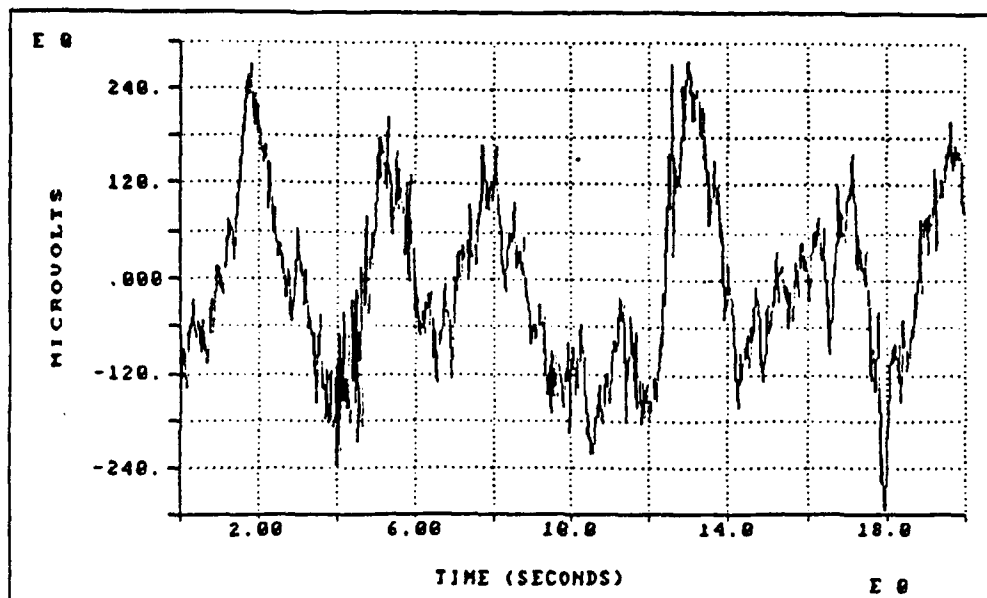
Figure 9   Very High Amplitude, Very Low Frequency
Delta Band Brain Wave (13:1024)

Example of fronto-temporal electroencephalogram (recorded
also with subdermal electrodes) during 20 seconds of the
immediate post-emesis period of motion sickness. Note the
high level of low frequency activity (delta wave band < 3
Hz, with most activity at frequencies < 0.5 Hz) at ampli-
tudes of several hundred microvolts. The subject is very
symptomatic and at rest.

diphenyl-2, 4-imidazolidinedione) is a barbiturate-like drug

having a five-membered ring that is capable of suppressing

or eliminating the occurrence of seizures (convulsions) in

humans due to epilepsy through the apparent inhibition of

the spread of seizure activity in the motor cortex of the

brain (4:1541). Phenytoin, which is marketed commercially

as Dilantin, is known to be very safe, producing very few,

if any, side effects in those who take it. It has even

shown evidence experimentally of increasing the ability to

concentrate and think logically. It has the following
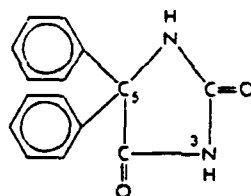
structure:

Figure 10   Phenytoin (58:452)

and is a hydantoin derivative whose chemical name is

diphenylhydantoin (6:951; 7:254-255; 49:300; 58:452).

Phenytoin is taken orally in capsule form to achieve a

normal serum level between 10 and 20 mcg/ml. The method by

which phenytoin inhibits the spread of seizure activity

within the brain appears to be by stabilizing the threshold

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of membranes (sodium and calcium ion conductors) against hyperexcitability caused by excessive stimulation or environmental changes. Phenytoin has been used successfully by epileptics since 1938 when its anticonvulsant activity was discovered by Tracy J. Putnam and H. Houston Merritt (4:1541; 21:814-815; 26:81, 810; 54:498; 58:452). Two "placebo-controlled, double-blind crossover" tests were conducted in 1987. During those tests, the two subjects were each spun in the chair twice, once while on a placebo and once while on phenytoin, with neither knowing which time they were on phenytoin. While on phenytoin, the subjects displayed a 600 percent increase in tolerance (see Table 4) to motion sickness and showed no measurable signs of any side effects (13:1022-1023; 53:10-11).

The results were so encouraging that the AFIT team changed its direction of research in 1988, abandoning, at least for the moment, biofeedback and began to study drug therapy in earnest using phenytoin. This was a significant event as the group was now trying to identify and control the cause rather than trying to minimize and control the effect. The results obtained in 1988 by Captains Morales and Scott were quite interesting (see Table 5 on page 56). Three subjects (numbers 3, 4 and 6) remained asymptomatic throughout their trials. The other four subjects experienced at least a 300% time increase in their ability

Table 4 1987 Phenytoin Study Results
(9; 13:1024-1025; 53:11)

Subject	Blood Serum Level	Symptom-Free-Time (In Minutes)		Time-To-Emesis (In Minutes)		RPM
		Placebo	Phenytoin	Placebo	Phenytoin	
1	unk*	3.0	40.0	8.0	48.0	unk
2	urk	4.0	65.0	12.0	72.0	unk

* unk = unknown

Table 5   1988 Phenytoin Study Results
(9; 13:1024-1025; 53:67-68)

Subject	Blood Serum Level	Symptom-Free-Time (In Minutes)		Time-To-Emesis (In Minutes)		RPM
		Placebo	Phenytoin	Placebo	Phenytoin	
1	14.7	1.0	2.6	2.0	6.0	14
2	12.0	3.0	32.5	4.0	42.0	14
3	12.3	5.0	68.0 (asym*)	13.0	68.0 (asym)	16
4	12.3	17.0	99.0 (asym)	38.0	99.0 (asym)	16
5	14.0	1.0	21.0	6.6	26.3	17
6	12.4	3.0	70.0 (asym)	8.3	70.0 (asym)	18
7	13.0	1.5	43.5	14.0	54.0	18

*asym - asymptomatic; subject never reached emesis; trial
    stopped

to delay reaching emesis. The combined results of 1987 and 1988, shown in Table 6 on page 58, begin to give a good indication of phenytoin's potential in combating motion sickness. The one obvious shortcoming of the work done by Morales and Scott is the small sample size of only seven subjects. Even when added to the two subjects from 1987 (total of nine) the data could not be considered conclusive or absolute, just very encouraging (9; 13:1023-1024; 53:66-69).

Another exciting aspect of the work that was done in 1988 was the fairly successful development of mathematical models, through the use of computer software. The software was used to correlate the biophysiological data being recorded to the symptom levels actually reported by test subjects using a number scale of 1 to 10, with 1 being asymptomatic and 10 being emesis (53:70-106; 64:ii, 47-52).

        1989.

Captain Russel B. Smith began work on the motion sickness problem in 1989. Captain Smith tried to determine if there was a statistically significant relationship between phenytoin serum levels and frontal-midline EEG signals using a cepstral analysis technique. His findings did not substantiate such a relationship (66:viii, 23, 38-60). He also continued to evaluate the effect of phenytoin in inhibiting the onset of motion sickness. By the end of

Table 6   Combined 1987 and 1988
Phenytoin Study Results
(9; 13:1024-1025; 53:11, 67-68)

Subject	Blood Serum Level	Symptom-Free-Time (In Minutes)		Time-To-Emesis (In Minutes)		RPM
		Placebo	Phenytoin	Placebo	Phenytoin	
1	unk*	3.0	40.0	8.0	48.0	unk
2	unk	4.0	65.0	12.0	72.0	unk
3	14.7	1.0	2.6	2.0	6.0	14
4	12.0	3.0	32.5	4.0	42.0	14
5	12.3	5.0	68.0 (asym#)	13.0	68.0 (asym)	16
6	12.3	17.0	99.0 (asym)	38.0	99.0 (asym)	16
7	14.0	1.0	21.0	6.6	26.3	17
8	12.4	3.0	70.0 (asym)	8.3	70.0 (asym)	18
9	13.0	1.5	43.5	14.0	54.0	18

*unk - unknown
#asym - asymptomatic; subject never reached emesis; trial
     stopped

1989, a total of 21 subjects had participated in the experimentation to determine phenytoin's efficacy on motion sickness. The most valid results that had been produced using the most current and reliable sensors along with more standardized procedures were outstanding as depicted in Table 7 (11:1; 13:1023-1025). A greater than six times (600%) mean increase in tolerance to motion sickness had been the result of using phenytoin, which was an increase of over 200% above any other single agent (drug) currently in use. It was reasonable to credit phenytoin with this improvement as adaptation was not a likely factor. In fact, the subjects' time to nausea while on placebo was within 10% of that observed during their susceptibility trials. Not only had the use of phenytoin greatly increased the test subjects' ability to delay or even prevent the onset of motion sickness, its use, unlike other drugs used to combat motion sickness (both individually and in combination) such as dramamine, scopolamine, promethazine, and dexedrine, had been marked by a relative absence of disorientation, blurred vision, dizziness, drowsiness, sedation, and dry mouth which are typically present as common, unwanted and possibly dangerous side effects (11:1; 13:1022-1023; 17:468-470; 20:84; 66:6-7). In fact, the only significant side effects that were commonly encountered were a direct result of the subjects' extended time in the chair -- sore buttocks and

Table 7 Phenytoin Study Results Through 1989
(9; 13:1024-1025; 53:11, 67-68)

Subject	Blood Serum Level	Symptom-Free-Time (In Minutes)		Time-To-Emesis (In Minutes)		RPM
		Placebo	Phenytoin	Placebo	Phenytoin	
1	unk*	3.0	40.0	8.0	48.0	unk
2	unk	4.0	65.0	12.0	72.0	unk
3	14.7	1.0	2.6	2.0	6.0	14
4	12.0	3.0	32.5	4.0	42.0	14
5	12.3	5.0	68.0 (asym#)	13.0	68.0 (asym)	16
6	12.3	17.0	99.0 (asym)	38.0	99.0 (asym)	16
7	14.0	1.0	21.0	6.6	26.3	17
8	12.4	3.0	70.0 (asym)	8.3	70.0 (asym)	18
9	13.0	1.5	43.5	14.0	54.0	18
10	10.4	10.5	13.3	20.5	36.2	22
11	11.4	2.5	12.3	5.6	15.2	20
12	12.0	2.8	3.6	7.0	9.5	16
13	10.1	2.5	4.0	3.8	5.2	18
14	11.7	0.7	4.0	5.8	6.0	18
15	17.3	6.5	6.7	12.0	17.0	18
16	18.2	1.3	11.7	4.0	14.5	10
17	23.9	2.3	90.0 (asym)	8.0	90.0 (asym)	13
18	15.1	3.3	36.0	14.8	60.6 (symp$)	12
19	16.4	2.1	19.8	6.0	21.0	12
20	18.5	1.6	6.0	5.3	15.5	13
21	16.2	6.3	9.2	14.0	22.3	18

*unk - unknown; #asym - asymptomatic, subject never reached emesis, trial stopped; $symp - symptoms experienced, subject never reached emesis, trial stopped

discomfort from the sensors. The test subjects' cognitive and sensory abilities as well as their physical performances were not measurably affected or degraded by the drug (6:949, 951; 7:254-255; 13:1022-1025; 65:207-211).

Ongoing Research

AFIT motion sickness research has also spawned work outside the school. While a student at AFIT, Captain Daniel Gleason participated in the motion sickness studies as a subject. Captain Gleason was normally highly susceptible to coriolis stimulation, but did find some encouraging relief (over 250% more resistant) while on phenytoin.

His assignment after AFIT was to Edwards Air Force Base, CA, to perform flight testing. He was sick approximately 3 hours and 45 minutes of his first 4-hour flight after his arrival at Edwards. Captain Gleason decided there was no reason to get sick if there was a drug that could possibly prevent it or at least ease the symptoms. He approached the Flight Surgeon at Edwards, Major Kenneth D. Leckie, telling him about phenytoin and the research going on at AFIT. Major Leckie, himself highly susceptible to motion sickness, was very interested. He wrote the United States Air Force Systems Command Surgeon Generals Office seeking permission to perform operational testing of phenytoin on airsick flyers at Edwards.

Permission was granted to conduct the testing in September 1989. Only those flyers who were not in actual command or control of the aircraft or involved with navigation could become subjects. Three subjects (one flight surgeon and two flight test engineers) were selected; all three had a history of high susceptibility to motion sickness which had interfered with their operational testing programs. The protocol used was straightforward and simple. If a morning flight was planned, the dosage of phenytoin on the day prior was 400 mg, 300 mg, and 300 mg spread over the afternoon and evening with the last dose at bedtime. If an afternoon flight was scheduled, the dosing (again 3 doses) began that morning with the last dose taken around lunch. Blood samples were drawn to determine actual serum levels about one hour prior to each flight.

The results were outstanding. All three subjects exhibited excellent control over motion sickness while on phenytoin. Symptoms were either very mild (a little queasy once and a little lightheaded once) or absent and side effects were practically nonexistent. The serum levels were in the desired therapeutic range of 10-20 mcg/ml and there was no degradation in the subjects' ability to complete their assigned flight test duties. Further testing will follow (4:1541; 9; 38; 43).

Future Research

Other research is being planned based on the work at AFIT. Interest is high and results have been good -- therefore, AFIT-prompted experimentation using phenytoin is currently second in priority on the manifest schedule for the shuttle program's DoD initiative, Military Man In Space (MMIS), and is tentatively scheduled to occur in 1992 or 1993. Rockwell International is responsible for the development of the Payload Integration Plan to support the mission.

Electroencephalogram (EEG) Signals

Electroencephalogram (EEG) signals can be defined as:

A graphic record of the electrical activity of the brain as recorded by the electroencephalograph (1:421).

It is important to understand what EEG signals are, what types there are, and where they come from when preparing to analyze color-coded topographic mappings of them. This background allows the analyzer to understand what is being seen. With this in mind, the source of EEG signals, the brain, will be reviewed first. After that, EEG signals themselves will be discussed and their relationship to motion sickness and epilepsy will be discussed.

The Source.

The source of EEG signals is the brain. The brain is a

very complex organ and a good beginning for discussing it is to look at its structure. Figures 11 through 15, on pages 65 through 69, provide a pictorial view of the brain with various parts, "landmarks," identified and, in some cases, explained. Figure 15 is displayed to provide additional insight into the structure of the brain and will not be talked to directly.

The "landmarks" are arbitrary in nature, but are quite useful as demarcation points. Figure 11 shows where the brain is located relative to the head and skull. Figure 12 depicts and describes those structures that surround (cover) the brain. The brain is composed of gyri (ridges) and sulci (valleys). Figure 13 identifies many of the brain's most prominent "landmarks." Essentially, humans have two brains: a right hemisphere and a left hemisphere. The two hemispheres are nearly identical in appearance and are separated by the longitudinal sulcus, which runs from the front of the brain to the back. The Sylvian fissure, another sulcus, runs along the outer side of each hemisphere. A third sulcus, the central fissure, runs downward from the top of each hemisphere over the outer portion of that hemisphere until it intersects the Sylvian fissure (61:8-11).

Each hemisphere is divided into four major areas, or "lobes," with the Sylvian and central fissures acting as
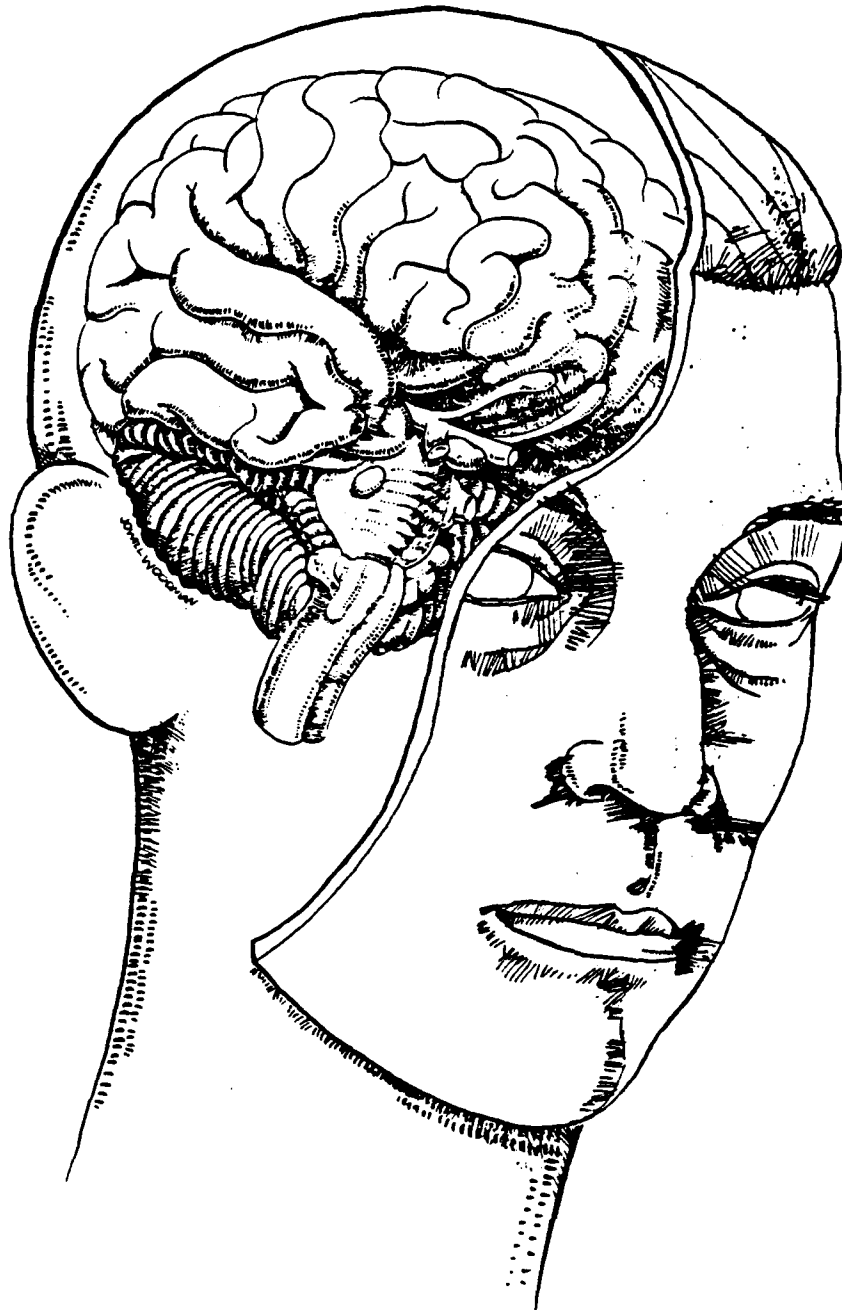
Figure 11   Location of the Brain (61:11)

CRANIAL BONE

DURA MATER

DURAL SINUS

CEREBROSPINAL FLUID
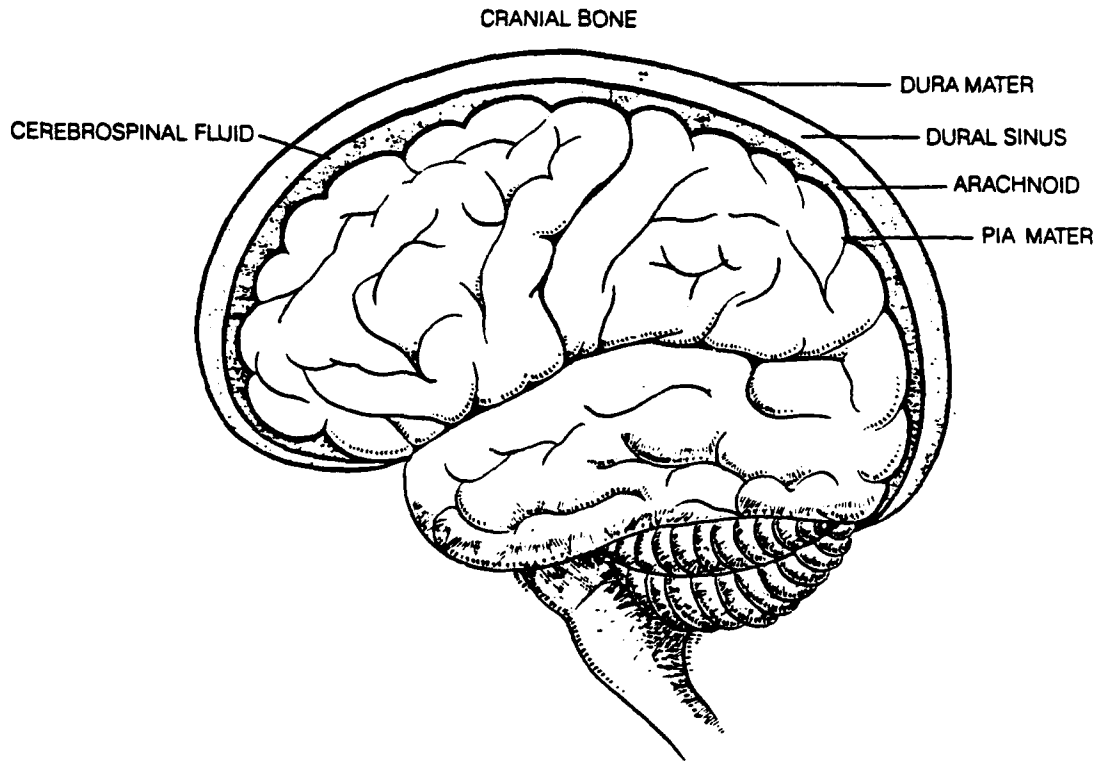
ARACHNOID

PIA MATER

Figure 12   Protective Material Surrounding the Brain
(61:8)

If you lift the hard, bony canopy of the skull (the
cranial bone), you first encounter three membranes, each
with Latin names: the outer dura mater (hard mother); the
second, the arachnoid (cobweb); the third, pia mater (tender
mother).

The dura is a hard, fibrous enclosing membrane just
beneath the bony skull.

The arachnoid bridges the brain's many crevices, a fact
some fanciful early neuroscientists compared to the vaulting
of a spider's web.

The pia is molded with the firmness and tightness of a
gymnast's outfit, designed to dip into every irregularity on
the brain's surface.

Between the pia and the arachnoid flows cerebrospinal
fluid, which winds like a vast network of rivers, filling
every one of the brain's gullies. The total amount of cere-
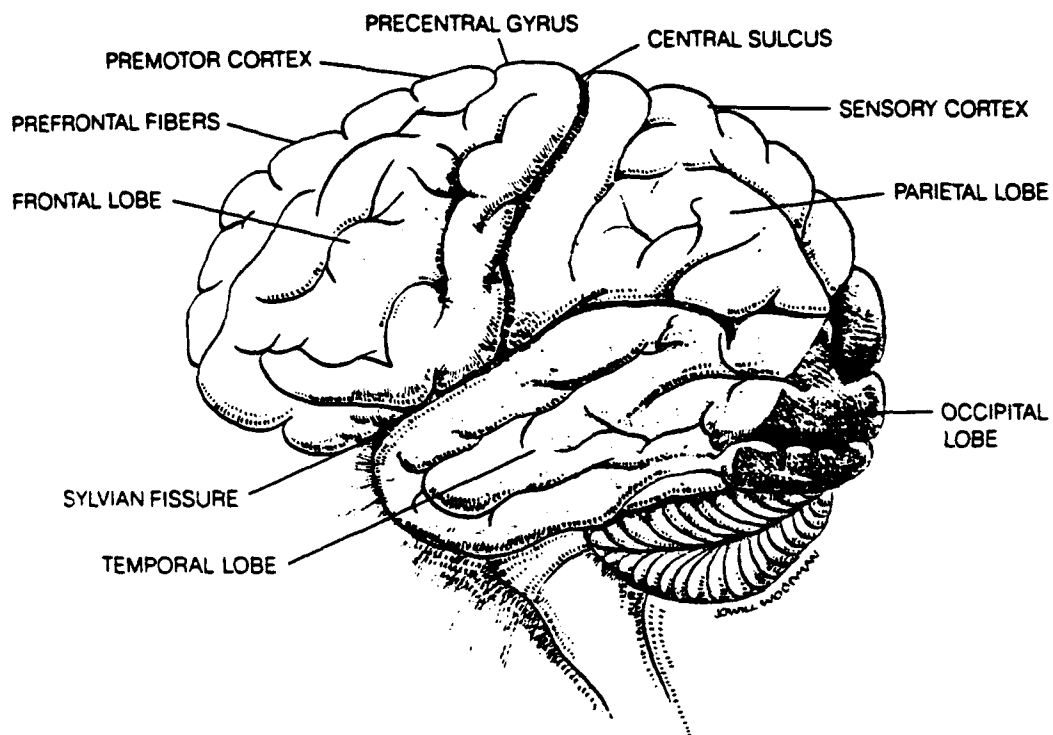brospinal fluid in the brain is only about 120 milliliters.
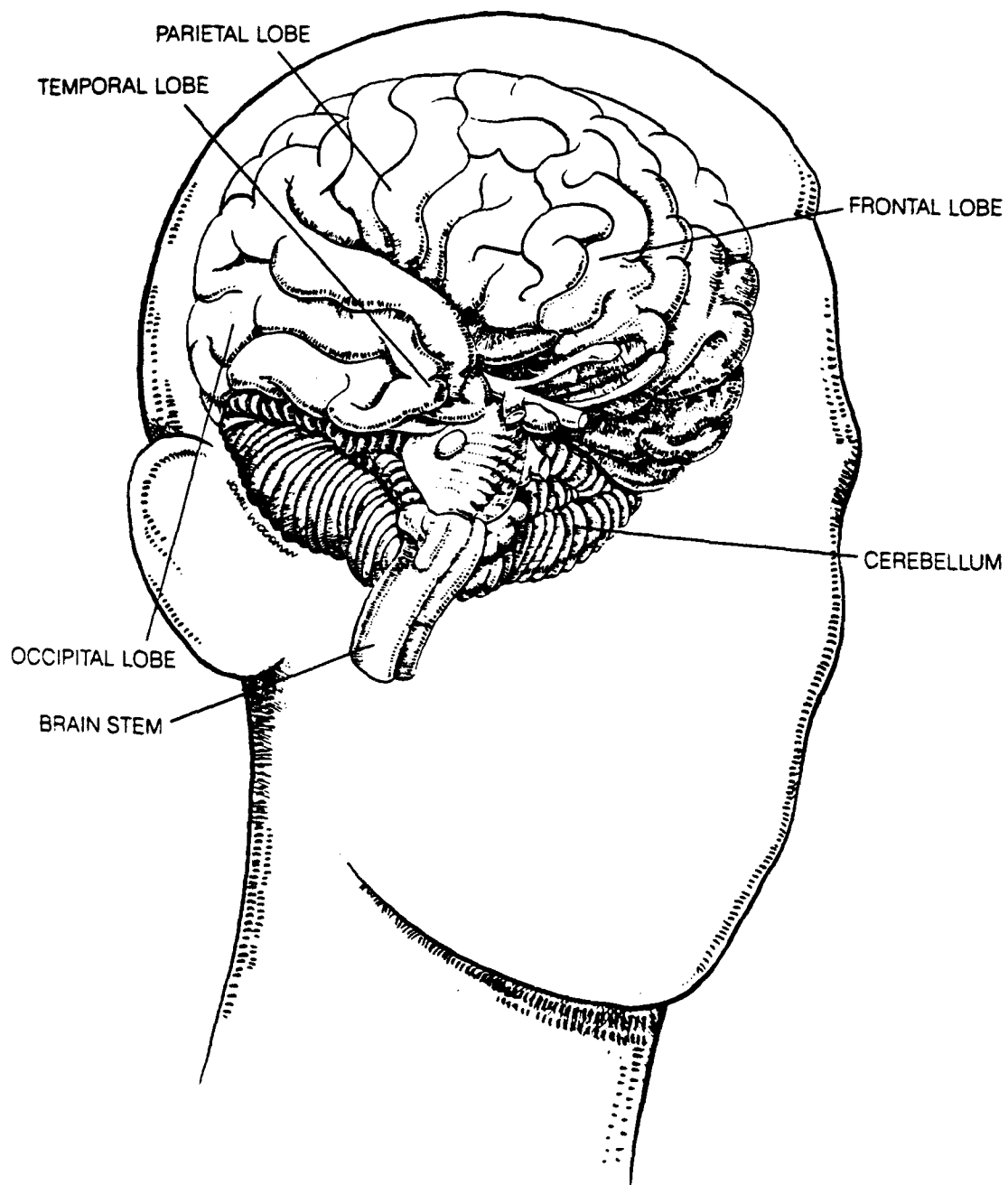
Figure 13   Areas ("Landmarks") of Cerebral Cortex (61:9)

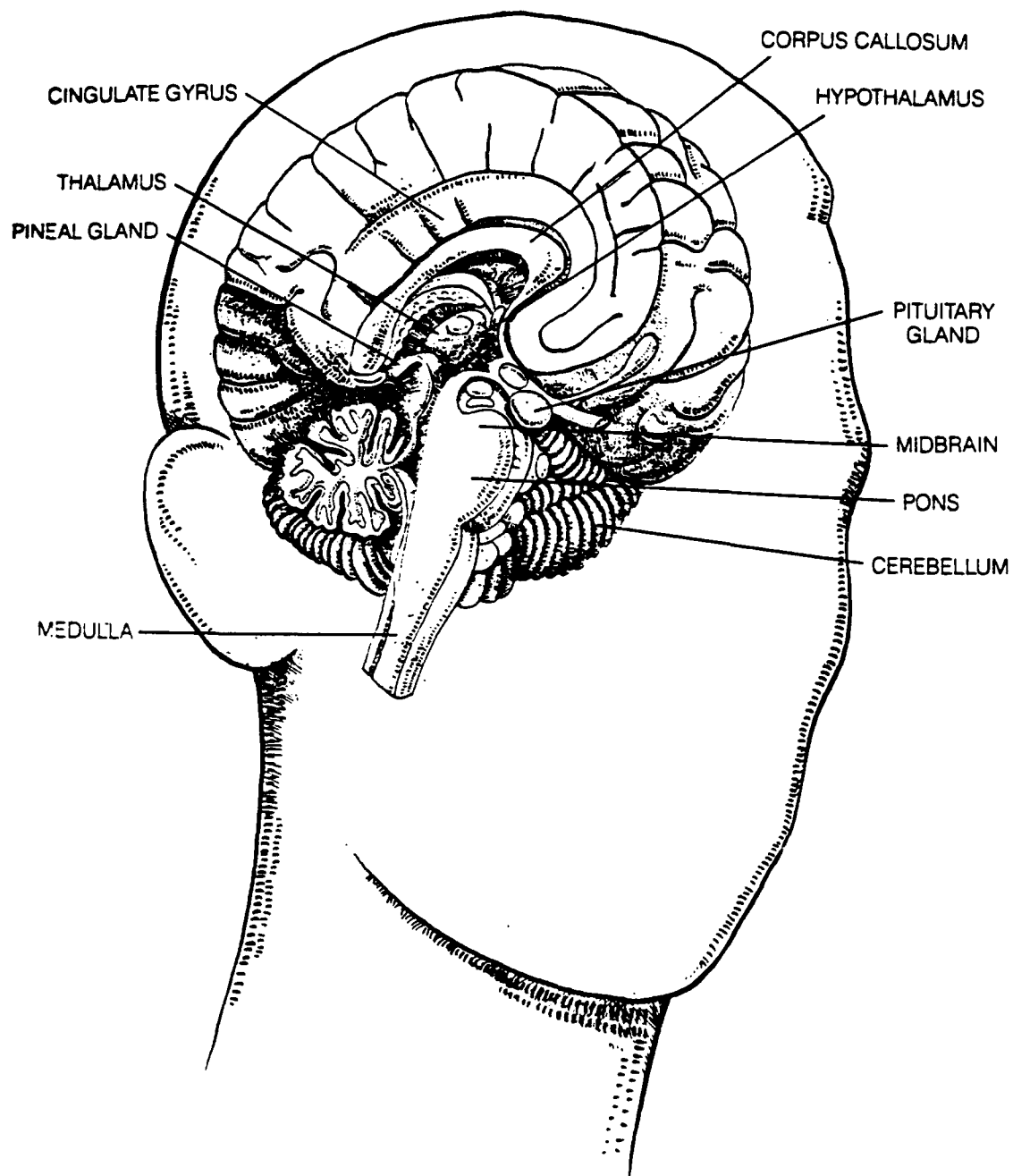**Figure 14 Major External Structures of the Brain (61:13)**

Figure 15 Inner Brain Structure (Cutaway View) (61:15)

boundaries. Figures 13 and 14 illustrate the positions of these lobes. The four lobes are located as follows: frontal lobe, everything in front of the central fissure that is above the Sylvian fissure; parietal and occipital lobes, behind the central fissure and generally above the Sylvian fissure with the parietal lobe coming first; and the temporal lobe, which is generally considered to be everything below the Sylvian fissure (61:9-13).

One of the primary objectives of this thesis is to use topographical mappings to attempt to see if motion sickness onset and progression in EEG terms is possible to trace. The mapping of activity, as recorded on the scalp using subdermal electrodes, is potentially just a mapping of activity in (or at least on the surface of) the four lobes of each hemisphere. It is reasonable to assume that the recorded signals would differ in polarity, frequency, and/or amplitude if the electrodes were placed in different cortical layers (versus the cortical surface or subdermally on the skull). Potential fluctuations, driven by synaptic activity, appear to have a spatial distribution within the cortex (39:631-632; 67:7). It is hoped that activity from other areas such as the brain stem are not included as it would be incorrectly attributed to a specific area on the cortical surface. If, therefore, a pattern can be observed, it is important to know which part of which lobe is being

affected and what the primary functions of that area are, as currently known. This knowledge may provide insight into the possible causes and/or cures for motion sickness. At least one would hope to understand what areas are being affected and be able to associate them with the observed symptoms and reactions of people experiencing motion sickness. It is therefore important to have a basic understanding of the primary functions of the four lobes.

Within the frontal lobe lie the precentral gyrus, the premotor cortex, and the prefrontal fibers (see Figure 13, page 67). The precentral gyrus is the primary area that controls movement of the opposite side of the body -- the left hemisphere controls the right side of the body and the right hemisphere controls the left side of the body. The premotor cortex area's primary function appears to be the organization of complex motor movements. The prefrontal fibers appear to be the area that help inhibit our behavior. They help provide the control necessary for us to act in a socially acceptable manner (61:10).

The primary "sensory cortex," which receives somesthetic inputs from all of the body's sensory receptors (except the eyes and ears), is located in the parietal lobe. This area has been designated the "feeling" part of the brain and is organized quite precisely. Within the postcentral gyrus (as opposed to the earlier discussed precentral gyrus), there is

an area that corresponds to each particular part of the body (again, except for the eyes and ears). This one-to-one correspondence allows us to identify exactly where on our body a sensory input (touch, pain, pressure, muscle and tendon tension, etc.) is received (38; 61:11-12).

The temporal lobe's primary functions include memory of complex events, hearing, and self-realization. The memory experiences of déjà vu and jamais vu appear to originate consequent to stimulation of this area. It appears the sense of individuality arises from this area as well as the sense of time. It has been suggested that the temporal lobe is our link to the "old brain" or "animal brain" (limbic system) that we each possess. This is our link to other species and appears to allow us to experience basic, rudimentary emotions such as jealousy, fear, anger, and lust (61:12).

The occipital lobe encompasses the primary and secondary visual centers. It is the receiving area for stimuli that were received by receptors in the eye and transported down the optic nerve. This is where vision with meaning and understanding occurs as opposed to mere visual-chemical retinal vision. The signals are developed and interpreted in this area (61:12).

The Cause.

There are two principal types of cells that primarily

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compose the central nervous system, glia cells and nerve
cells (neurons). Glia cells, located between neurons, help
provide a structural integrity and contribute to field
potentials as well as acting as contact points for various
processes across the cells. It is, however, the neuron that
is of primary interest when discussing the origination of
EEG signals (67:1).

EEG signals ("brain waves") are presumed to be
consequent to the electrochemical communication that occurs
in the brain between neurons. Neurons have a unique
structure, as shown in Figure 16, and are specifically
suited to perform their role. As a nerve impulse travels
from neuron to neuron, it passes through the nerve body and
down the axon until it reaches a dendrite or a cell body
directly. It is at the membrane of the next neuron that
information is transferred. This information must be
transported over a gap, the synaptic cleft (not shown in
figure), of about a millionth of an inch (the synaptic cleft
is in the small circle labeled "Synapse" in Figure 16). Up
to the synaptic cleft, the propagation of the information
across the neuron has been via an electrical signal. This
electrical signal was the result of an action potential that
was triggered by a receptor's receipt of a stimulus that was
sufficient to overcome the neuron's resting potential (38;
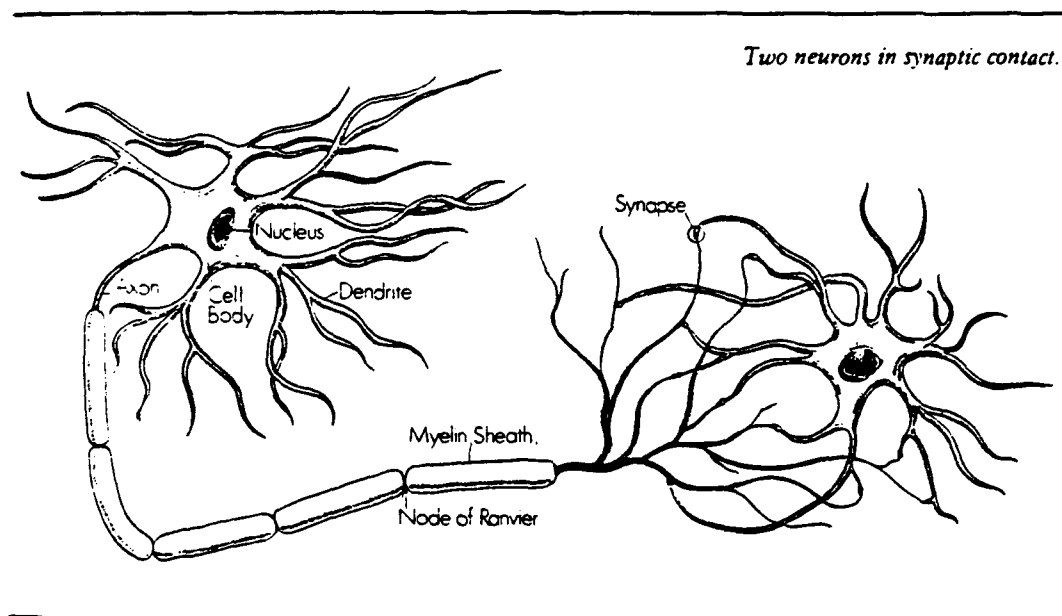61: 27, 29, 34).

Two neurons in synaptic contact.

Figure 16   Two Neurons in Synaptic Contact (61:27)

In order to cross the synaptic cleft, the electrical signal must be transformed into a chemical signal, thus giving neuronal communication its electrochemical properties. Communication across the synaptic cleft occurs when a sufficient amount of electrical signal (action potential) is received at the synapse to invoke the release of a neurotransmitter which is received by the next neuron. The neurotransmitter (acetylcholine or norepinephrine for example) is a chemical that is stored in vesicles along the presynaptic membrane. The small packet of neurotransmitter crosses the gap to a receptor on the postsynaptic membrane of the next neuron that is specifically designed to receive that particular type of neurotransmitter (chemical) and no other. It is at the postsynaptic membrane that the information is once again converted to an electrical signal, if enough stimuli are received. It is important to realize that not all information ("messages") passed from neuron to neuron are excitatory (orders to fire); in fact, most are inhibitory (reducing the likelihood of firing). This prevents a continuous "brain storm" of firings that would produce an ongoing epileptic convulsion (61:34-35).

The Signals.

The first recordings of the brain's electrical activity, using electrodes placed on the intact skull, were made over 60 years ago by Hans Berger in 1929. EEG signals have since

become invaluable in the study of the brain's functional states. They are also of great help in diagnosing injuries and functional disturbances of the brain. There are four basic types of EEG signals which may range from 0 to 300 microvolts on the surface of the scalp and are differentiated by their frequency ranges. The four types of signals are alpha, beta, delta, and theta (31:734, 736; 34:451).

Their approximate frequency bands are as follows:

Delta	0.0 -	3.0 Hz
Theta	3.0 -	8.0 Hz
Alpha	8.0 -	13.0 Hz
Beta	13.0 -	20.0 Hz

with the most obvious activity occurring in the alpha band. This activity is a rhythmic activity (essentially a sine wave) about 10 Hz. This sinusoidal shape is what makes "alpha bursts," as registered by an electroencephalograph, so readily identifiable. These bursts normally occur when the conscious subject becomes very relaxed with eyes closed (31: 734-735; 34:451).

There are many factors that influence the appearance of EEG signals. The following are some of these known factors:

1.   Location of the electrodes on the subject's skull;

2.   Subject's state of vigilance (conscious state);

3.   Age of the subject;

4.   Region of the subject's brain being recorded;

5. Hereditary traits of the subject;

6. Any non-normal influences on the subject's brain (injuries, functional disturbances, diseases, stimuli, chemical influences, drugs, etc.);

7. Any technical (caused by the recording equipment or surroundings, etc.) or biological (produced by the subject -- such as scalp-muscle activity, arterial pulsations, eye movements, heart signals, etc.) artifacts (31:734-735; 34:451).

As discussed previously, the 10-20 international system (see Figure 6, page 33) has been established to standardize the symmetrical placement of electrodes on a subject's skull. The state of the subject to produce "normal" EEG recordings has generally been accepted to be a restful consciousness (34:452). Typical wave forms for the four types of EEG signals are shown in Figure 17 (31:734).
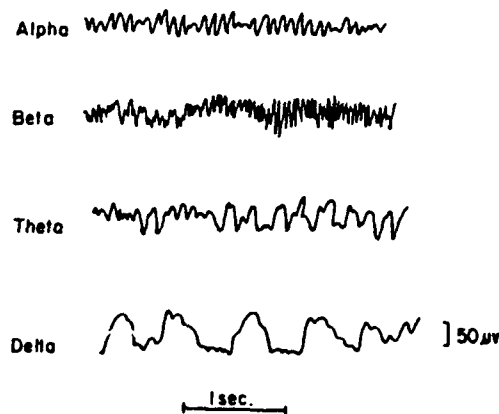

Figure 17 Typical Wave Forms of Four Basic EEG Signals (31:734)

Even for the trained neurophysiologist, the "ability to detect special patterns, changes, and differences is quite limited." Testing and experience have given evidence to the highly subjective nature of visual evaluation of EEG signals. For example, strong alpha activity with high variability (a wide spectral peak) can mask the presence of delta and theta activity if the signal is not appropriately broken down by frequency. The mere opening of the eyes can dramatically change (by eliminating the alpha rhythm) the recorded EEG signal as Figure 18 demonstrates.

Figure 18   Effect of Eyes on an Alpha Rhythm (31:735)

Even with all the possible variations, some general rules-of-thumb have been developed. There is a characteristic EEG appearance for each stage of sleep. The lower the age, the greater amount of low-frequency signals. EEG signals of children differ from those of adults. The more severe a brain injury, the more low-frequency activity that results. The same EEG signals may be caused by a wide array of different diseases and injuries. Many EEG signals are not disease or injury specific. Transient signals (spikes,

sharp waves, and spike-and-wave activity) may appear
spontaneously. The frequency of brainwaves increase as the
level of mental activity increases (31:735-736; 34:452).
Figures 19 through 24 on pages 79 through 84 illustrate a
variety of possible EEG signal patterns that may be seen.

It quickly becomes obvious that the amount of
variability in EEG signals is staggering. This variability
increases the difficulty in analyzing the signals.
Analyzing the effects of epilepsy, which is the most
important analysis performed on the human electroencepha-
logram, is an example that illustrates this difficulty.
Table 8 on page 85 lists the various seizure types that an
epileptic may experience. Notice the variability (Figures
19, 23 - 24) just within the signals associated with
epilepsy (grand mal, petit mal, and psychomotor seizures)
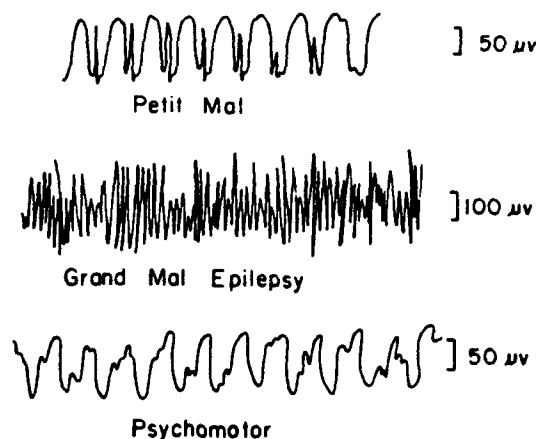that are illustrated.

Petit Mal

Grand Mal Epilepsy

Psychomotor

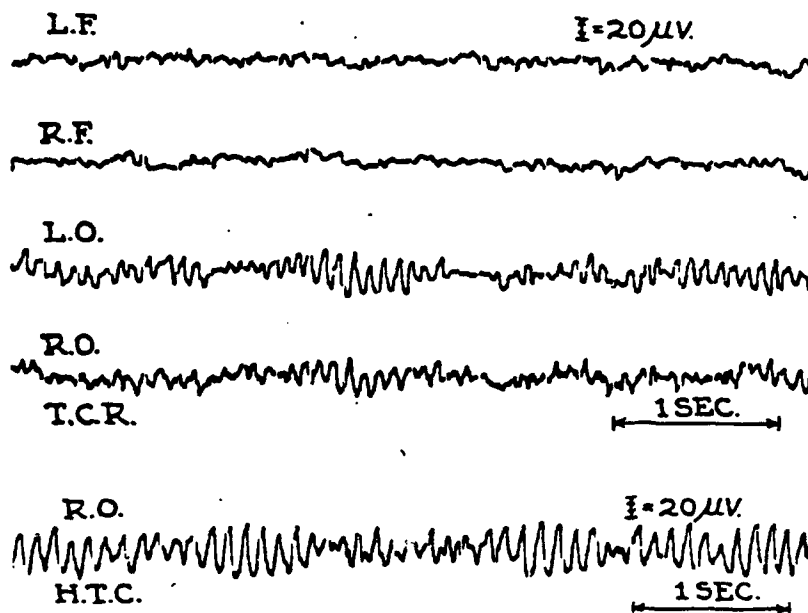**Figure 19 EEG Signals of Different Epilepsy Types (31:737)**

Figure 20   Normal Electroencephalogram of Frontal
             and Occipital Areas (63:484)

Amplification was equal for all leads.   Notice the greater
amplitude and lower frequency in the occipital records.

L.F. : Left Frontal Region
R.F. : Right Frontal Region
L.O. : Left Occipital Region
R.O. : Right Occipital Region

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EXCITED

RELAXED

DROWSY
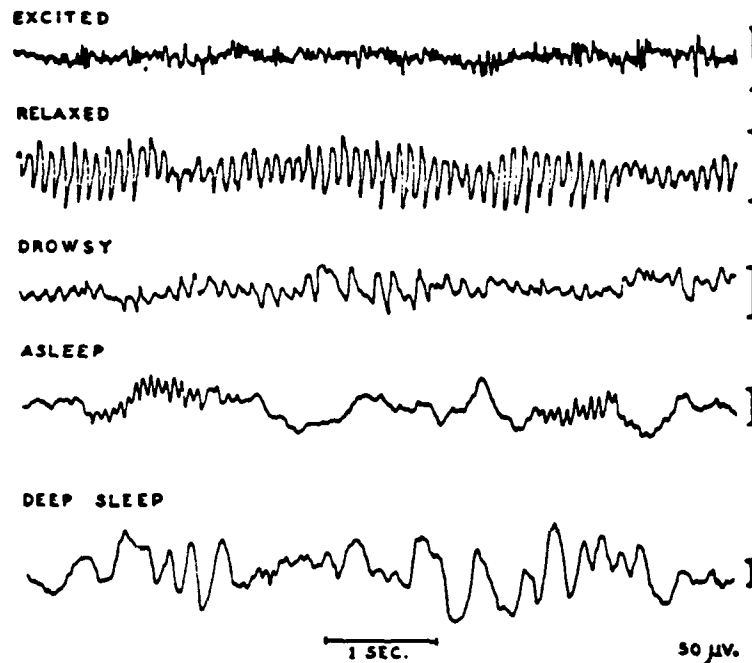
ASLEEP

DEEP SLEEP

1 SEC.   50 μv.

Figure 21   Selected EEG Records (63:485)

Note that excitement is characterized by a rapid frequency
and small amplitude and that varying degrees of sleep are
marked by increasing irregularity and by the appearance of
"slow waves."

adult, awake, frontal:

adult, awake, posterior:

adult, drowsy, posterior:

child, (2 years) awake:

100 μV

1 sec.
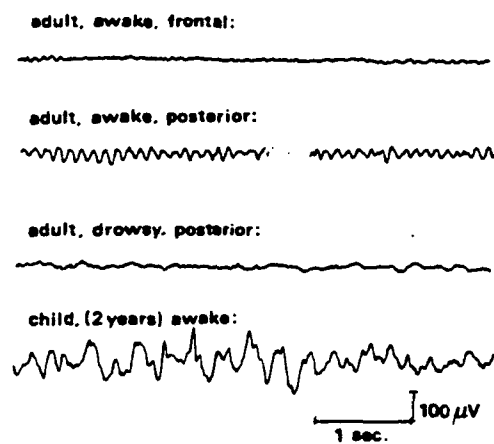
Figure 22 Recordings Showing the Great Variability of Normal EEG (34:452)

adult, awake:

abnormal delta activity (brain tumour)

spike- and wave- activity (epilepsy)

sharp waves (epilepsy)

100 μV

1 sec.
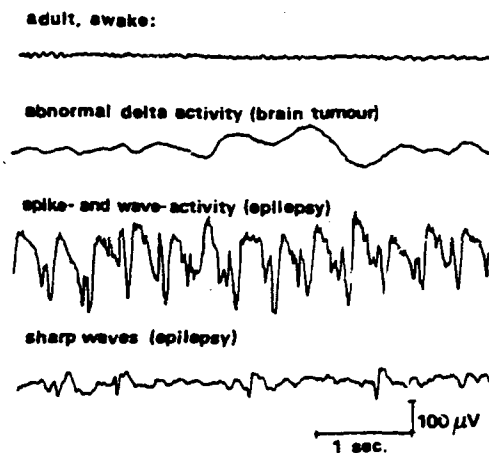
**Figure 23   One Normal EEG and Three Abnormal EEG Signals
(34:452)**

**Figure 24 EEG Signals of the Three Major Forms
of Epilepsy (63:486)**

Amplitude and time calibration is given at the right of each
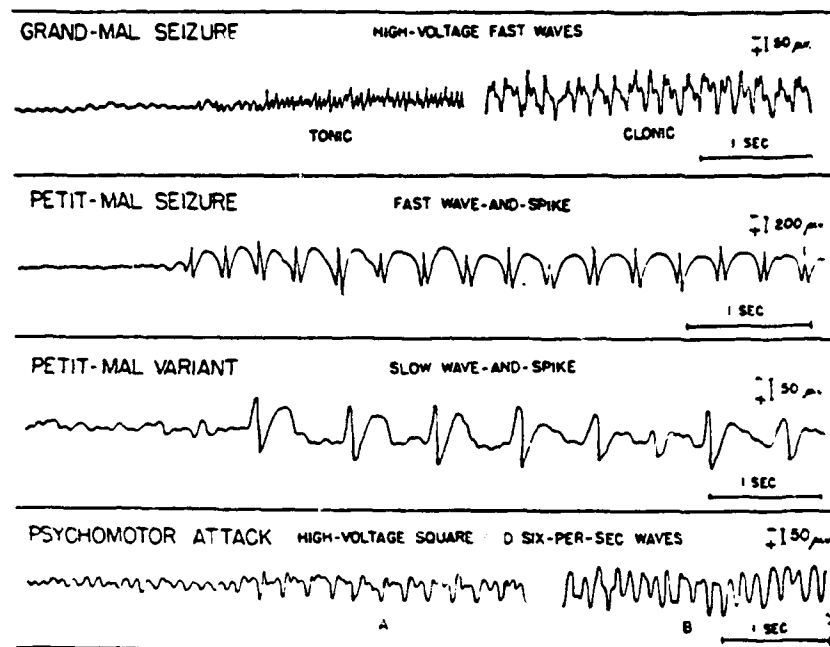strip. At the left of each strip, a small amount of pre-
attack record is shown. In the fourth strip, A is initial
phase of attack in which patient was dazed and quiet, and B
is a later phase in which patient was talking excitedly and
making coarse voluntary movements.

Table 8   Classification of Epileptic Seizures* (58:449)

SEIZURE TYPE †		CHARACTERISTICS
I. *Partial Seizures* (Focal Seizures)	A. Partial seizures with elementary symptomatology (*cortical focal*)	Various manifestations, generally without impairment of consciousness, including convulsions confined to a single limb or muscle group (*Jacksonian motor epilepsy*), specific and localized sensory disturbances (*Jacksonian sensory epilepsy*), and other limited signs and symptoms depending upon the particular cortical area producing the abnormal discharge
	B. Partial seizures with complex symptomatology (*temporal lobe, psychomotor*)	Attacks of confused behavior, generally with impairment of consciousness, with a wide variety of clinical manifestations, associated with bizarre generalized EEG activity during the seizure but with evidence of anterior temporal lobe focal abnormalities even in the interseizure period in many cases
	C. Partial seizures secondarily generalized	
II. *Generalized Seizures* (Bilateral, Symmetrical Seizures)	A. Absences (*petit mal*)	Brief and abrupt loss of consciousness associated with high-voltage, bilaterally synchronous, 3-per-second spike-and-wave pattern in the EEG, usually with some symmetrical clonic motor activity varying from eyelid blinking to jerking of the entire body, sometimes with no motor activity
	B. Bilateral massive epileptic myoclonus	Isolated clonic jerks associated with brief bursts of multiple spikes in the EEG
	C. Infantile spasms	Progressive disorder in infants with motor spasms or other convulsive signs, bizarre diffuse changes in the interseizure EEG (hypsarhythmia), and progressive mental deterioration
	D. Clonic seizures	In young children, rhythmic clonic contractions of all muscles, loss of consciousness, and marked autonomic manifestations
	E. Tonic seizures	In young children, opisthotonus, loss of consciousness, and marked autonomic manifestations
	F. Tonic-clonic seizures (*grand mal*)	Major convulsions, usually a sequence of maximal tonic spasm of all body musculature followed by synchronous clonic jerking and a prolonged depression of all central functions
	G. Atonic seizures	Loss of postural tone, with sagging of the head or falling
	H. Akinetic seizures	Impairment of consciousness and complete relaxation of all musculature, secondary to excessive inhibitory discharge

* Modified from the International Classification of Epileptic Seizures (Gastaut, 1970).

† Some classifications include unilateral seizures as a distinct category. Additional seizure types are presently unclassified due to incomplete data.

Rer mber that it was earlier stated that some of the EEG
signals (particularly in the low delta region with a very
high amplitude and very low frequency) occurring during
motion sickness resembled those that sometimes occur during
a psychomotor/partial seizure. It has been hypothesized
that the brain may be experiencing a seizure-like phenomenon
during the onset and progression of motion sickness.
Research in this area, to correlate the brain waves of
epileptics to those of motion-sick individuals, is ongoing
at AFIT (10:1-10).

Brain Mapping

What is Happening?

Topographical color mapping of the brain's electrical
activity is an attempt to convert recorded EEG signals from
their typical linear black ink tracings to a more
informative, more discernible, easily interpreted colored
map in the shape of the skull (either a side or top-down
view). The maps that are produced are the end-product of a
series of processes. The processes are physiological,
electronic, and mathematical in nature. These processes are
susceptible to various forms of artifact, distortion, and
error which can be caused by the equipment, the software,
the investigators, or even the subjects. The assumption
underlying topographic mapping is that there exists a

"normal" mapping for subjects and that it can be readily identified. It is also, therefore, assumed that any abnormality would be evident and identifiable (39:628).

The basic procedure involves the placement of electrodes (sensors) in a variation of the international 10-20 placement system (Figure 6, page 33) on or in (subdermal) the scalp. EEG signals are recorded from these points, passed through amplifiers and low-pass filters, run through an A-to-D converter, and loaded into a computer. A power spectrum containing numerical values for the amount of power in specific frequency bands is generated for the recorded electrode locations and a paradigm in the selected software interpolates between the points to produce a complete map. Of course, prior to all of this, the system needs to be carefully calibrated from end to end. It would seem to be an obvious advantage to have as many equally spaced (approximately equidistant) electrodes as possible to equalize the effects of the interpolation algorithm (44:176; 56:125).

Common Problems and Considerations.

As discussed previously, there are many possible sources of error and confusion in this type of research. Many aspects of the procedures must be closely monitored to include: artifact minimization, subject cooperation, data collection parameters, reference choice, ground choice,

number of leads used, map resolution, map generation, display parameters, and map interpretation. One additional step (a "sanity" check) must be taken to ensure that a viable mapping is produced. A comparison must be made between the black ink EEG paper tracing and the resultant map to see if what the map indicates makes sense based on the recorded tracings (39:628-629; 56:125).

Artifact minimization begins with the conscious state of the subject which can significantly alter the recorded EEG signals. The ideal situation is to have the subject in the same conscious state for every trial. Of course, this can be difficult to do, but the subject can aid this effort. Conscious eye movement, eye blinks, and nystagmus can also impact EEG signals greatly. One method of trying to reduce this effect is to tape the eyes shut and then blindfold the subject. This type of artifact is most prevalent in the delta and theta bands, but may also occur in the alpha and beta regimes, and is predictably evident in the frontal regions (33:47, 50-51; 39:630-631; 44:176).

Muscle artifact is also a concern and primarily contaminates the beta band. It usually originates from the frontal and temporal areas and can be reduced by appropriate filtering. There are other sources of artifact (both direct and indirect) that can be equally or more detrimental to the accuracy of the collected data. Some of these sources are

respiration, throat movement, heartbeat, poor electrode
contact, sweating, laboratory temperature, electrical
connections, electrical "noise," computer processing,
spatial and temporal smearing of latencies and amplitudes,
spatial aliasing, baseline corrections, digital filtering,
A-to-D conversion, active references and grounds, and
ambient electrical fields (60 Hz alternating current, for
example). And last, but not least, one must remember that
these signals must travel a fair distance through a salt
water solution, tissue, bone, and skin just to reach the
electrodes. It is reasonable to expect some artifact and
electrical potential diffusion to accompany this journey
(33:12, 45, 52; 39:630-631; 56:125).

The system must achieve a stable gain that differs
little between channels and the differential amplifiers have
high common mode rejection. The amplifiers also need to be
low-noise and precisely matched with the ability to resolve
both slow and fast components. The stable gain should allow
for the exclusion of channel asymmetries caused by amplifier
interference or overload (16:2).

Selection of the data collecting parameters is
instrumental in determining what is mapped and how it is
mapped. To begin with, the data are normally recorded using
a differential (bipolar or referential/monopolar) technique.
The bipolar technique takes into account the difference

between two active scalp electrodes while the referential technique is concerned with the difference between an inactive electrode (the reference electrode) and an active scalp electrode. After recording, the Fast Fourier Transform (FFT) is the most common technique used for spectral analysis of continuous EEG data. However, FFT resolution is limited by the inverse of the sampling rate and the epoch size. The period (or epoch) of the sampling rate is the data collection period. Therefore, a five second epoch (sampling window) can discriminate down to 0.2 Hz and a two second epoch can only discriminate down to 0.5 Hz (9; 33:12; 39:629; 44:176).

Three rules must be remembered when selecting the sampling rate. First, the sampling rate must be at least twice the maximum frequency component (the Nyquist Criterion) or some of the signal's information will be lost. Some data (information) would be lost if a 200 Hz signal was sampled at a rate less than 400 Hz, for example. Second, aliasing must be prevented by selecting a sampling rate such that no frequency component of the signal is greater than 0.5 of the sampling rate. Aliasing occurs when a signal component's frequency is greater than 0.5 of the sampling rate and the component presents itself at a lower frequency. Sampling 70 Hz muscle activity at 100 Hz could cause the muscle activity to alias to 30 Hz, for example. The use of

a sharply attenuated, high-frequency (low-pass) filter can minimize aliasing. Third, the epoch (sampling period) must be long enough to ensure a representative sample of the data under study is attained (9; 39:629).

Prior to Fourier analysis, the electrical potentials that are received by the scalp electrodes are amplified and filtered. The voltages at each amplifier (filter) output are measured at regular intervals (sampling rate) by the computer and are converted to digital codes which are stored in the computer serially. These stored data are then analyzed. The analysis produces amplitude coefficients (usually the study parameters) associated with each of the frequency bins (0 Hz, 0.5 Hz, 1.0 Hz, etc.). The bins are then summed together in four groupings which correspond to those frequency bands (group of bins) generally assigned as alpha, beta, delta, and theta (39:629).

Usually, the investigators are interested in a continuous stream of EEG data, not just one epoch. Therefore, EEG data are reflected as a series of contiguous epochs, one right after the other, with each epoch analyzed separately. Because EEG signals are constantly changing, the results for each epoch are averaged and presented as a series of mappings, each with a duration equal to the epoch length. Subject cooperation (as discussed previously) is very important, as changes in attention (mental state),

physical position, or conscious state can greatly alter the averaged result since spectral analysis is quite sensitive to these forms of EEG signal change (39:629).

Topographic maps require that the EEG signals used be recorded using a reference point. There are three primary types of references that are generally used: a linked-ears differential reference, a common-average differential reference, and a local (source-derivation) differential reference. Using linked ears (ear lobes) as the reference point is one commonly used method, but this method is not without flaw. The ear lobes can reflect (and thereby cancel) part of the temporal lobe activity being recorded because of their proximity to nearby temporal electrode sites. The resultant low amplitude area is a direct result of the ear lobes not being "inert" or "inactive" references. Using the ear lobes as a reference may also distort the head's electrical fields (9; 33:12; 39:630; 56:125; 62:20).

Cerebral reference sites such as the vertex (Cz) can be used if a possible loss of acuity in measuring activity near the reference is acceptable and some other region is of primary interest. One drawback to this procedure is the possible registration of activity in other leads due to high amplitude activity at the reference location (39:630). Other locations such as the forehead, chin, nose, cheeks, neck, and shoulder have been tried as references, but none

have proven to be completely acceptable. Artifacts caused by muscle activity, eye movement and blinking (nystagmus), respiration, throat movement, sweating, and heartbeat (EKG) can affect the utility of these sites as reference locations. It should be noted, however, that the mastoid has been used successfully as a reference by some investigators and is one example of an often used referential reference point (9; 27:372; 33:12; 39:630-631).

A final option in the search for a reference point is to use a pooled reference such as the common-average reference or the local (source-derivation) reference. One concern with the use of these techniques is that high-amplitude focal activity will be transposed to distant, physiologically neutral regions, thereby adding to the complexity of interpreting the resultant maps. The source-derivation reference often proves superior to the common-average reference. This is due to the fact that when large transients are distributed over the electrodes, it usually is not influenced by the "dipole" effect. The fidelity and accuracy of activity registration is usually superior with this method also. The referential montage reference scheme, which utilizes a single reference lead, appears to offer some advantage over pooled reference schemes. Data for a pooled reference scheme can be mathematically recomputed from a referential montage reference scheme while the

converse is not true. No matter what reference point (and ground location) is chosen, one key consideration that must be observed is the need to minimize the impedances (usually less than 5000 ohms) at these contact points. For this reason, subdermal electrodes often work the best. However, large surface electrodes on a well prepared surface can also have very low resistances (9; 27:372; 33:12, 45; 39:630; 56:119; 62:20).

The decision of whether or not to use a ground must first be made before location of the ground is determined. If the need for a ground exists, then great care must be taken to identify an electrically inert reference location. The ground can help eliminate 60 Hz interference that, as discussed before, may appear as artifact. An improperly placed ground, however, may pick up EKG signals that will contaminate the EEG data (9; 33:7, 45, 52, 180).

The number of leads (electrodes) used is also a critical consideration because of the very nature of the data collection. Because of the required interpolation between leads, it is important to employ as many leads as possible. The number of leads can be constrained by many factors. Some of these factors are cost of amplifiers and filters, difficulty in constructing unique amplifiers and filters, computer limitations to store and process data, difficulty in positioning amplifiers, subject discomfort caused by the

placement (and number) of electrodes, accuracy and speed of electrode placement, and the ability to maintain good electrode contact during the investigation. Some researchers have reported using as many as 64 leads per hemisphere. Leads should be concentrated over the area(s) of interest, if feasible. Even when concentrated, the data are limited as only a few actual points of data, corresponding to the number of leads used, are being recorded. Most of the values displayed in the map are the result of interpolation computations between these points. This is in sharp contrast to the more commonly used computer tomographic (CT) and magnetic resonance imaging (MRI) scans which it resembles. The CT and MRI scans have a real data point corresponding to each pixel on the display with little redundancy (39:631-632; 55:312).

The placement of the electrodes also affects the amplitude of the recorded scalp EEG. It appears the amplitude increases to some extent as the interelectrode distance increases. Using curve fitting, it has been discovered that the relationship between scalp EEG voltage and interelectrode distance can be accurately characterized by a simple mathematical equation. It has been found that a first-order exponential equation can provide a high degree of accuracy while reproducing the required concave and asymptotic behavior. Curve fitting was simplified through

the application of logarithmic transformations. The
equation has the form

$$Y = A(1 - e^{-BX})$$

with Y = amplitude (voltage) and X = interelectrode
distance. A and B are constants that are calculated for the
total spectrum and for each frequency band by using the
least-squares regression method in an iterative manner
(19:287, 289).

Resolution increases as the number of leads increases,
but is still limited to general areas rather than specific
points due to interpolation limitations and the signal's own
journey. Another limitation to the resolution achieved is
the number of pixels used to generate the maps. A commonly
used amount is 4800 pixels, but this number can vary
greatly. It is important to remember that a topographical
map is merely a 2-D representation of a 3-D process (16:2;
27:373; 39:632; 55:312).

The generation of maps to provide this 2-D perspective
carries an inherent error in that some areas of the scalp
are not represented true to their physical nature. Some
areas are under-represented while others are over-
represented. The transference from scalp to computer map
may not be a one-for-one transfer physically as area size
integrity may not be maintained. Some areas will be reduced
in size (compressed) and others will be larger (stretched).

Projections that have the most utility are those that provide approximate equal-area representations for most of the scalp areas (39:632).

The two most commonly used projections are the superior view and the lateral view. Using the superior view (looking down onto the top of the head), both hemispheres can be viewed simultaneously and a good look at the top of the head (frontal and parietal lobes) can be had. One drawback to this method is the possible loss or distortion of data from either the temporal or occipital lobes. The lateral view (from the side) provides a good look at only one hemisphere at a time. This produces great detail on the temporal lobes, but can greatly distort or lose information regarding the other lobes. Another shortcoming of using the lateral view is its inability to provide the investigator the opportunity to compare the right hemisphere to the left hemisphere. The ability to assess the symmetry of brain activity in the two hemispheres can be a very important and useful tool. The choice of the projection type used is driven by the requirement (or lack thereof) of symmetrical analysis and the location of the area under study (3 :632).

An error that may occur during the generation of a map results from a problem of interpolation. As mentioned previously, interpolation plays an important role in generating the maps, but it suffers from the fact that many

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of the electrodes lie at the edge of the electrode array (on the perimeter). Edge effects caused by not having equidistant neighboring electrodes on each side can produce distortion around the boundary of the map. This problem can be difficult to overcome (39:632).

There are two algorithms generally used for interpolation: the 2-D spline algorithm and the 4-nearest neighbors algorithm. Spline functions can be differentiated to allow for the computation of scalp current density surfaces and are usually estimated more accurately. The spline algorithm also usually produces a smoother interpolation surface with the extrema not located at the electrode sites necessarily (27:373; 44:176). In both cases, information is assembled from multiple EEG leads by creating power spectral arrays from all electrode sites simultaneously. The map that is produced at that moment gives an overall picture of the electrical brain activity at that corresponding period in time. This map is a composite resulting from the combination of the recorded data (44:176).

Choosing the correct scaling parameters can make a topographical map quite clear and easy to read. The desired frequency ranges can be chosen for display and analysis.

Typical frequency ranges that may be used are:

0.0	to	3.0 Hz	Delta Band
3.0	to	8.0 Hz	Theta Band
8.0	to	13.0 Hz	Alpha Band
13.0	to	20.0 Hz	Beta Band

(31:734-735; 34:451; 39:633; 44:178).

The desired energy (amplitude) ranges can also be selected. Ranges such as 0 μV to 31.8 μV and 0 μV to 63.7 μV, etc., can be used and are often depicted as color bar charts. These charts are often divided into 16 or 32 equal regions (bins) that extend from the minimum value to the maximum value of the selected range. Each region is represented by a different color (or a variation of color due to changes in texture). Dark red or white often represent maximum values while dark blue or black often represent minimum values. These colors are portrayed on the topographical maps. The activity (energy) levels observed on the maps can be determined by matching the colors to their corresponding regions of the color bar chart. Color scale consistency is very important (16:1; 39:633).

The selection of scaling parameters is somewhat subjective. Different frequency band selections should be tested to ensure enough data are represented to give a good mapping without losing any significant data or overextending the width of any band. An example of this may be whether to

set the alpha band from 7.0 to 12.0 Hz or 8.0 to 13.0 Hz or some combination of the two (23:491; 39:633).

The choice of the energy scale parameters determines whether any data are lost (truncated) due to the maximum and minimum values selected. A small range may allow for close scrutiny of minor changes, but may not reflect most of the data, thereby overemphasizing these minor changes. A large range has the opposite problem as it may reflect a majority of the data, but small, subtle changes may go unnoticed. It should be noted that it is also possible to scale and observe data based on their power spectrum (composition) instead of their energy (amplitude), but this method doesn't seem to correlate as well with routine visual inspection. Great care must be taken when comparing different pieces of data if different scales (or types of scales) were chosen for them (23:491, 493; 39:633; 55:312; 56:125).

As the subject of topographic map interpretation is about to be discussed, it is appropriate to review a few of the characteristics underlying the map that is pictured on the screen. Brain mapping is an inexact science. The pictured map is a composite of a series of various, distinct, often almost arbitrary, processes. The first is the conscious state and cooperation of the subject. The second is the EEG signals themselves and the inexact, questionable signals that are reaching the scalp. The next

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is the limited number of electrodes used, their less-than-optimum placement, and the limited paradigm of interpolation used. Selection of the collection parameters is another variable. The noncontinuous nature of the analysis is also a factor. The choices of reference and ground affect the data. The selection of what view or projection (superior versus lateral) to use affects the analysis and how the data are presented. The choice of scaling parameters alters the presentation of results. And finally, it must be noted again that a mapping is a 2-D representation of a 3-D surface event.

Map interpretation is a very detailed, involved process that is very susceptible (and prone) to error and misunderstanding. It is a great advantage to the interpreter to have a substantial background in electroencephalography and knowledge of the function and structure of the brain along with a full understanding of the software and hardware being used. The interpreter needs to be able to assess the clinical significance of topographic changes, be familiar with the effects on the frequency spectrum of various EEG changes, and be able to identify possible artifact sources that may skew the analysis. It is also important (as mentioned previously) that the results (data) be reviewed (sanity checked) at each intermediate step (23:493; 39:634-635).

The common practice when interpreting data is to use a "normative" database that has been collected separately (possibly by someone else) as the basis for comparison. But again, the question arises, "What is normal?" Some basic parameters such as age, sex, handedness, eyes open, eyes closed, amount of medication administered, and room temperature (environment) can be controlled fairly well, but these are only a small percentage of the factors that influence the production of EEG signals. The careful selection of subjects and the ability to minimize the subtle differences between the subjects (such as different locations or mean values of alpha activity) can enhance the chances of ascertaining a normal baseline from which to compare. Also, the techniques, equipment, and procedures used must be uniform for both the database and the investigative studies. After all these considerations, the maps are looked at to note the amplitude (energy) or power in given frequency bands. The origin and propagation patterns, if either exist, are also noted as well as the areas of the brain that correspond to them. From these observations, diagnosis may be made, or hypotheses as to the cause or treatment of observed behavior may be drawn (23:493; 39:634; 44:178).

IV. Data Acquisition

Challenges Encountered

Relocation of Laboratory.

The motion sickness laboratory was relocated from Room 150 to Room 242 in Building 640 in December 1989. The 21-year-old rotating chair and control console used in previous motion sickness research were salvaged (sold to the highest bidder). The workbench and desk were dispersed. All other equipment (16-channel strip chart recorder, etc.), materials, supplies, tools, texts, and subject data had to be relocated to the new laboratory. This required that the new lab be established and set up. This was a very time consuming exercise.

Installation and Testing of the New Chair and Support Equipment.

The new rotating chair system arrived in February 1990 and was installed. The chair was modified to allow for the mounting of sensor hardware. Two metal plates were attached to the back to support the batteries and the Astropulse 90 expired CO_2 monitor. Attachment points were mounted for the monitor and the bank of circuit boards that connect to and receive imput from the various physiological sensors. The interconnections between the sensors, the circuit boards,

the strip chart recorder, the data display computer, and the Beta tape recorders all had to be wired and tested.

Design and Construction of New Equipment.

Dr. William Chelen designed and constructed the miniature, self-contained, head-mounted, 14-channel EEG amplifier box that made the research possible. He also assembled the 14 platinum sensor array and its mounting that plug into the amplifier box. A new 14-channel, low-pass filter bank was also designed and built by Chelen to correspond to the 14-channel EEG amplifiers (sensors).

Brain Mapper.

A Bio-logic computer system (including brain mapper) has now been incorporated in the data analysis system. Both the correct setup and proper learning of its use were painstakingly difficult; calibration and setup were complicated because of the custom nature of the Bio-logic system used at AFIT. Initially, the correct peak-to-peak voltage (.4 volts) and wave shape (square wave) for calibration had to be experimentally determined. The system had to be calibrated prior to each use with all 14 channels being done so simultaneously. This required the setup of 14 different connections. A junction box has now been constructed to simplify the simultaneous calibration of all the channels. The correct defaults to accept the calibration signals had not been loaded in the software by

the manufacturer and had to be reset by the investigators.
The accompanying manual was incomplete and had many errors.
No schematics were sent with the system. Even getting data
loaded into the system from the Beta tape recorders proved
difficult at first.

It took a great deal of work to learn how to read and
analyze the data as they were presented by the Bio-logic
system. The Bio-logic system's default display shows
electroencephalographic data in the following regimes:

0.0 - 3.5 Hz	Delta Band
4.0 - 7.5 Hz	Theta Band
8.0 - 11.5 Hz	Alpha Band
12.0 - 15.5 Hz	Beta Band

using 2 second epochs (windows); therefore, the sampling
rate had a period (P) = 2 seconds. Remembering that P =
$1/f$, with f = frequency, $1/f$ = 2 seconds and f = 0.5 Hz.
Therefore, the minimum frequency actually being registered
was in the range of 0.5 Hz, not 0.0 Hz as it appeared. This
difference was significant as frequencies in the very low
delta band were of particular interest. To partially
overcome this problem, the four regimes were set as follows:

0.0 - 3.0 Hz	Delta Band
(0.5 - 3.0 Hz in reality)	
3.0 - 8.0 Hz	Theta Band

8.0 - 13.0 Hz   Alpha Band

            13.0 - 20.0 Hz   Beta Band

with the data processed at normal speed. To record/display
/register the very low delta band signals, the data rate was
sped up to 6 times normal speed (by speeding up the playback
speed of the Beta instrumentation tape recorder) with the
lowest regime still set to: 0.0 - 3.0 Hz delta band (0.0833
- 0.5 Hz in reality), with the other three regimes ignored.
This produced a total of five mappings for each point in
time of interest. Even with the adjustment of speeding up
the data rate, some data may have still been lost in the
very low delta band. This could not be overcome as there
were limitations to the practical amount the data could be
sped up and still be processed and analyzed accurately.
Also, a speed increase of 6 times provided an exact
crossover point at 0.5 Hz for the two delta band maps. It
was also believed that if any data below 0.0833 Hz were
lost, that the amount was small and could be overlooked.
The choice of 20 Hz as the maximum frequency component
analyzed was consistent with the established beta range of
interest. It was believed that there was little activity
above that level. It also makes sense since the Bio-logic
system can only accept and process signal elements up to
23.5 Hz (for a normal range of 0.5 - 23.5 Hz).

It also was a challenge to determine which subdermal
sensor positions actually corresponded to which sensor
positions as displayed. It was critical to be consistent
from the electrodes (montage) to the Beta tape to the data
input junction box to the montage array selected as the new
data file was loaded into the Bio-logic computer system.
This was accomplished through trial and error, position by
position, by referencing the particular montage used on a
given subject. Learning what was being seen and from where
allowed the system to be used for analysis.

Data Acquired

Data were acquired on 8 subjects during the course of
this research in 1990. Of these 8 subjects, 3 completed
both trials (phenytoin vs placebo) using the acute-dosing
method, 1 completed both trials using the extended-dosing
method, 3 subjects were data-gathering only trials, and 1
subject was an extended-dosing phenytoin-only trial (see
Table 9). One of the data-gathering only trials (Subject
1) was of an investigator doing the initial testing run of
the new 14-channel EEG sensors. Another was of a subject
(7) who was rejected for the phenytoin trial during the
initial examination performed by Chelen because of a medical
problem. He was allowed, at his request, to continue with a
data-gathering only trial to be used as a source of
additional EEG data.

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Table 9 1990 Study Results

Subject (Dosing Method)	Blood Serum Level	Symptom-Free-Time (In Minutes)		Time-To-Emesis (In Minutes)		RPM
		Placebo	Phenytoin	Placebo	Phenytoin	
1 (N/A)	N/A	0.5	N/A	1.3	N/A	14
2 (Ac#)	16.3	0.8	2.3	10.3	10.8	10
3 (Ac)	15.0	2.0	4.0	13.1	13.8	14
4 (Ac)	14.5	3.5	65.0 (asym$)	14.5	65.0 (asym)	14
5 (Ex*)	8.9	1.2	6.1	41.1	57.3	10
6 (Ex)	9.8	N/A	0.5	N/A	6.7	13
7 (N/A)	N/A	1.0	N/A	4.7	N/A	14
8 (N/A)	N/A	0.2	N/A	1.5	N/A	20

#Ac - acute dosing method
*Ex - extended dosing method
$asym - asymptomatic; subject never reached emesis; trial
        stopped

Subject 8 had previously completed both trials in 1989. He was used to collect EEG data while a new modification to the head-mounted amplifier box was being tested. The modification included the installation of a switch which allowed for the use of either a referential reference or a local reference. His data were the first recorded at AFIT using a local differential reference. Another unique aspect of this subject's trial was that no reference ground on the subject was used. The modification, was in part, in response to an apparent synchronicity of EEG records that was noticed in the EEG recordings of Subject 7. During a review of the trial records of previous subjects, this apparent synchronicity was identified to be intermittently present in some of them. The synchronicity may be attributable to a sweat artifact due to the use of a silver-silver chloride ground electrode. The possible sweat artifact appears to be contaminating the natural brain EEG. Although such a possible sweat artifact would mask the natural brain EEG to some extent, electrode-to-electrode potentials can be recovered with the use of differential amplification which cancels common signals. Only further investigation can lead to a definitive answer to this problem; however, it should be noted that no synchronicity was observed during this trial (33:52).

The extended-dosing phenytoin-only trial was of an individual (Subject 6) who had previously completed both trials as a subject using the acute-dosing method. This trial was conducted to see if the subject's symptom-free-time and time-to-emesis while on phenytoin could be increased using the extended-dosing procedure, thereby testing the earlier stated hypothesis of the investigators. The results were inconclusive, as neither time was increased (in fact, both were less), but the blood sample drawn prior to the trial revealed the phenytoin content in the subject was sub-therapeutic. It took a few tries to accurately learn the correct sequence and dosing amounts to administer during extended dosing. More subjects will have to complete trials under both dosing methods to gain any meaningful comparison. One advantage of the data collected in 1990 was the elimination of head motion artifacts (through the use of the new chair and new EEG sensors and amplifiers) that had persisted since the inception of the motion sickness research at AFIT (Figure 25) (13:1023).

Phenytoin Efficacy.

There were four subjects who completed both trials. Of these four, the data from one subject (Subject 5) showed improved performance while on phenytoin, but his results were incomplete as his blood level of phenytoin was in the sub-therapeutic range. This subject was the first to be

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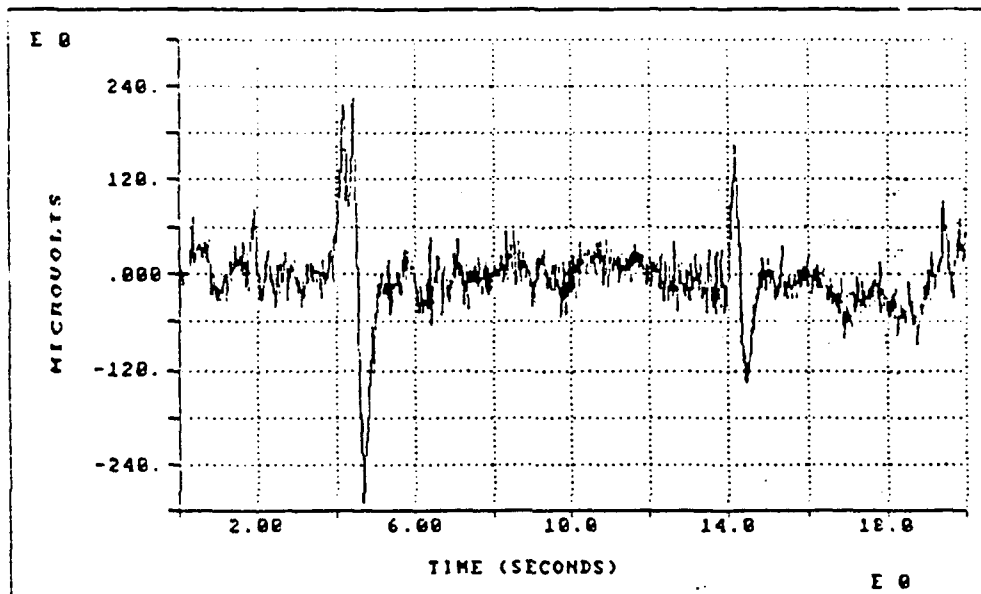
Figure 25   Head Motion Artifacts (13:1023)

Fronto-temporal (F8/T4) electroencephalogram recorded
with subdermal electrodes for 20 seconds during the begin-
ning of coriolis stimulation. Note the head motion arti-
facts beginning at 4 and 14 seconds and the absence of
obvious delta wave activity.

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given the extended-dosing treatment. Two subjects (Subjects 2 and 3) with therapeutic phenytoin levels showed an increase in their symptom-free-times while on phenytoin versus the placebo, but both had times-to-emesis that showed no statistical improvement between trials. Both of these subjects complained of side effects (reduced auditory acuity, dizziness, and disorientation) that may be attributed to the dosing method used (acute). Subject 4 realized the ultimate goal of this research and remained asymptomatic throughout the phenytoin trial (see Table 9, page 108).

Brainwave Mapping Patterns.

Twelve trial records were produced from the eight subjects who were used during the course of this research in 1990. The data from only four trials were considered usable. These four trials appeared to be the most artifact free. Two of the four were phenytoin trials (Subjects 5 and 6) and two were placebo trials (Subjects 1 and 8). A systemic grounding problem caused the measured EKG signals to bleed into the EEG data and contaminate all the EEG bands of three trials and produced some artifact in others. The position of the system ground was tested at several locations: the upper left chest, the left shoulder, the base of the left side of the neck, the middle of the left side of the neck, and the top of the left side of the neck, until it

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was finally placed on the center of the forehead. Various positions were successful with different subjects, but it was believed that the forehead position would work for all subjects, thereby removing the guesswork of the individual ground placement in the future. However, as mentioned previously, testing has begun on the possibility of using no ground at all (Subject 8).

EEG data were also lost during three trials when electrodes (reference and/or montage) became disconnected midway through them. The possible sweat artifact (synchronicity) invalidated the trial results of Subject 7 and also produced concern about a few of the other trials. The trial of Subject 4 (where he remained asymptomatic throughout) was not evaluated in this thesis because there was no origination or progression of motion sickness symptoms.

As a result, the data chosen for analysis were from three of the single trials and from one subject who completed both trials. Although not of the same two people, these data provided two complete trials of both phenytoin and placebo for use in pattern analysis.

All four of the trials chosen for analysis employed the same basic procedure and setup, but there were differences in ground and reference selection. Subject 1 was fitted with a ground on his upper left chest and a mastoid

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referential differential reference. Subjects 5 and 6 also had mastoid references, but their grounds were located on the centers of their foreheads. And finally, as stated earlier, Subject 8 was quite unique in that a local differential reference was used with no ground.

V. Results

Phenytoin vs Placebo

The results of the 1990 Phenytoin studies are shown in Table 9 on page 108. The four subjects who completed both trials demonstrated a mean increase of 99% in their times-to-emesis and a mean increase of 613% in their symptom-free-times. This despite one subject having a sub-therapeutic phenytoin blood level, another having his trial stopped because he was still asymptomatic after 65 minutes, and two others whose bodies apparently could not properly adjust to phenytoin under an acute dosing scheme. Another benefit of phenytoin was the ability of all the subjects under treatment to recover very quickly after completing their trials. All felt fine and considered themselves to be back to normal within a few minutes.

Analysis of Brain Mapper Patterns

Before pattern analysis can begin on the four chosen trials, it must be noted that great care must be taken to be aware of what energy (amplitude) scale is being used when reviewing a map. Subjects 1 and 8 demonstrated what could be considered the expected trend using the chosen frequency ranges. Both exhibited more activity in the theta and alpha bands and less in the beta band. In both cases, the same

energy scale could be used for the theta and alpha bands with the next lower scale used for the beta band. Although the scales were different between the two subjects (Subject #1 used 0.0 to 63.7 μV while Subject 8 used 0.0 to 15.9 μV for the theta and alpha bands) the relative relationships between the three bands were similiar. When comparing between different subjects, it is important to remember that the relative magnitudes (energy levels) of the mapped activity is not as important as the frequency range it is in and its location in the brain.

Subjects 5 and 6 had such large dynamic ranges of amplitude that the energy scale had to be adjusted frequently. This was caused in part by the unusually high beta activity that was often being recorded while the alpha activity was unexpectedly low. This phenomenon was present in the recordings of both subjects, but was more prevalent for Subject 6. Upon further study, it was discovered that both subjects were producing a lot of alpha activity, but at a frequency of about 14 Hz. Because of the frequency ranges that were chosen for analysis, this alpha activity was being registered as beta activity. This resulted in the over-representation of beta activity and the under-representation of alpha activity during portions of the mappings. Because of the intermittent nature of this occurrence and for the sake of consistency, the frequency ranges were not altered

for these two subjects. Besides, the most important issue
is the location of the activity in the brain, not its
frequency. Frequency range designations are somewhat
arbitrary and are really most useful as standardized
demarcation points for clinical research. The nominal
energy ranges used in this research were as follows:

Subject Number	Theta Band 3.0 - 8.0 Hz	Alpha Band 8.0 - 13.0 Hz	Beta Band 13.0 - 20.0 Hz
1	0.0 - 63.7 μV	0.0 - 63.7 μV	0.0 - 31.8 μV
5	0.0 - 31.8 μV	0.0 - 15.9 μV	0.0 - 31.8 μV
	0.0 - 63.7 μV	0.0 - 31.8 μV	0.0 - 63.7 μV
6	0.0 - 31.8 μV	0.0 - 31.8 μV	0.0 - 31.8 μV
		0.0 - 63.7 μV	0.0 - 63.7 μV
8	0.0 - 15.9 μV	0.0 - 15.9 μV	0.0 - 7.9 μV

with the most appropriate amplitude range selected for each
mapping. In instances where an individual map in a group
exceeds the scale, except during symptom level 9 - 10, it
should be understood that it has been verified that it
exceeds the scale by only a small amount (< 12 on 0.0 to
31.8 μV scale, for example) and that the chosen scale
provides the most suitable energy range color scale for
analysis.

The data were reviewed in several ways to detect
artifacts and then relatively artifact-free sections of data
were selected for analysis and mapping. Annotations were

made in a journal and on the strip chart during each trial
that noted detectable artifact occurrences. The raw data
recordings on the strip chart were reviewed as well as the
data recordings transferred from the Beta tape to the Bio-
logic computer. This review led to the selection of what
were considered to be the most artifact-free sections of EEG
data that corresponded to the selected trial stages.
Although selected somewhat arbitrarily, it was believed that
the chosen sections were representative of what was
happening during those segments of the trial. Because a
firm distinction could not be made in some instances as to
whether an energy reading was the result of an actual signal
or of an artifact and the fact that the "best" data were
selected for mapping, there was no editing of the data
within each 24-second window. In all cases, it was
difficult to separate the data from the artifacts during
emesis. Therefore, the final mappings for all the subjects
are more symptom level 9 than 10.

Phenytoin vs Phenytoin.

When looking at the topographical maps of Subjects 5 and
6, a few details should be remembered about their trials.
Both generated considerable alpha activity, but with some
peculiarities. As mentioned before, both produced an
abundance of alpha at about 14 Hz, but Subject 6 produced
the most by far. Subject 5 produced an inordinate amount of

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alpha during head motions to the right. To be consistent and avoid any skewing of the results due to these unexplainable bursts of alpha activity, all mapped sections during symptom levels of Subject 5 are recordings from when his head was up, down, or to the left. Perhaps the phenytoin had an effect on the alpha activity of these two subjects. It is impossible to say at this time.

One last detail to mention is the fact that the trial length for Subject 5 was a couple of minutes short of an hour. He progressed to symptom level 4 in about 10 minutes and stayed in the symptom level range of 4 to 6 - 7 for about 45 minutes. He experienced a very rapid succession from symptom level 6-7 to emesis, experiencing a "mini-avalanche" at the end of his trial. Therefore, his mapping for symptom level 9-10 appears to have less energy than expected as it really was quite calm before the storm.

Table 10 lists the pages and sequences for the maps of Subjects 5 and 6 in Appendix D. In the records of both subjects, there appeared a tendency for an increase in energy in all frequency bands as the subject transitioned from baseline to emesis. Both subjects frequently experienced an energy increase in the occipital lobes that continued on into the temporal lobes and ended in the frontal lobes. There were many variations to this basic energy transition that occurred with no one unique pattern

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Table 10   Topographic Brain Maps (Phenytoin)

Phenytoin Trials

	Subject #5			Subject #6		
	3.0 to 8.0Hz	8.0 to 13.0Hz	13.0 to 20.0Hz	3.0 to 8.0Hz	8.0 to 13.0Hz	13.0 to 20.0Hz
Baseline - Sitting At Rest	166	172	178	184	190	196
Baseline - Spinning Prior to First HM	167	173	179	185	191	197
Symptom Level 2-3	168	174	180	186	192	198
Symptom Level 5	169	175	181	187	193	199
Symptom Level 7	170	176	182	188	194	200
Symptom Level 9-10	171	177	183	189	195	201

taking place consistently. These activity (energy)
transfers were consistent with the prior hypothesis that
motion sickness is similar to a partial seizure and were not
entirely unexpected. However, no distinct pattern of
propagation or origination point emerged from the analysis
of the data.

Placebo vs Placebo.

Subjects 1 and 8 also demonstrated the basic tendency to
exhibit an energy buildup in all frequency bands in the
occipital region with subsequent energy increases in the
temporal lobes and even up into the frontal lobes. In both
subjects, the frontal lobes showed the least energy
(activity). Table 11 lists the pages and sequences for the
maps of these subjects in Appendix D.

In both trials, energy levels in all freqency bands
tended to increase as the subject transitioned through the
various stages of the experiment towards emesis. Again,
this was not unexpected. It must be noted that throughout
the mappings of Subject 8 there appears a high energy
(relatively speaking) area at the back of the occipital
lobes. Whether this registration is a result of a natural
activity or of an artifact is indeterminable. The key is
that it is consistent and therefore does not hinder
analysis.

Table 11 Topographic Brain Maps (Placebo)

Placebo Trials

	Subject #1			Subject #8		
	3.0 to 8.0Hz	8.0 to 13.0Hz	13.0 to 20.0Hz	3.0 to 8.0Hz	8.0 to 13.0Hz	13.0 to 20.0Hz
Baseline - Sitting At Rest	202	208	214	220	226	232
Baseline - Spinning Prior to First HM	203	209	215	221	227	233
Symptom Level 2-3	204	210	216	222	228	234
Symptom Level 5	205	211	217	223	229	235
Symptom Level 7	206	212	218	224	230	236
Symptom Level 9-10	207	213	219	225	231	237

In both trials, and especially in that of Subject 1, the energy levels are a little high during the two baseline periods. This may be due to a high level of activity in the lab and a high level of interaction with the subjects, thereby increasing the attention and activity levels of the subjects.

One last item to note is the low activity registrations in the center of the scalp throughout the trial of Subject 8. One factor that may have contributed to lower the energy readings was the electrode montage. There were no electrodes placed down the center-line of the scalp so that area may have been underestimated. Another factor that may have helped produce this result was the use of a local reference, but it is impossible to tell at this time that it was anything but a natural phenomenon. This last factor (the relationship between interelectrode distance and activity energy levels), may also be responsible for Subject 8 having lower energy levels across the board compared to the other three subjects.

Despite the similarities between the two subjects and their basic EEG tendencies, no point of origination of changed EEG activity could be ascertained. Also, no consistent propagation pattern emerged or could be detected.

Overall.

For all four subjects, the most common scenario shows an energy buildup in the occipital region with a subsequent increase in energy along one or both of the temporal regions with the buildup in energy occasionally reaching the frontal lobes. In all four subjects, the occipital regions register the most activity while the frontal regions register the least. This trend could be due in part to the locations of the recording electrodes. They may be overemphasizing the occipital region and underemphasizing the frontal region. However, the occurrence of an energy buildup in the occipital regions and then a subsequent energy increase in the temporal regions while the frontal regions remain relatively inactive is not inconsistent with the hypothesized sequence of events that can occur during a partial seizure. Also, not inconsistent with the activity surrounding a partial seizure, the energy levels tended to increase as the subjects transitioned up through the various stages of the experiment towards emesis. It must be remembered that partial seizures are also frequently localized and can produce spiking and spike-and-wave activity.

Despite these common tendencies, no clearly evident point of origination or propagation pattern for motion sickness could be discerned in the brains of these four test

subjects. At times, the energy levels and patterns appeared to be almost random, but at other times there appeared to be a sense order in the recorded activity. Some of this sudden randomness may have been a result of some form of artifact or another, but it is impossible to tell at this time. Throughout it all, there was never enough consistency to warrant the identification of either a distinct origination point or propagation pattern. Therefore, it would be premature to try and claim either exists.

VI. Conclusions and Recommendations

The data continue to support the hypothesis that phenytoin can be used successfully to combat motion sickness. The development of a more complete picture of phenytoin's capabilities and potential requires the study of more subjects. The effects of different dosing sequences, as well as the proper dosing amounts, must be further explored. The question of acute versus extended dosing must also be answered.

Also, the protocol (procedures) should be amended to try and create more consistency between subjects to eliminate as many variables as possible besides just the presence or absence of phenytoin. Items such as subject diet, precise time of capsule ingestion, subject serum levels, and lab activity and temperature during trials could all be more standardized. The periods of time between the susceptibility test and the two trials should also be the same for everyone as should be time required to complete instrumentation of the subject and calibration of the equipment prior to each trial. It would even be nice if the rotation speed and length of rotation time could be the same for all subjects. Unfortunately, neither appears to be practical at this time due to different levels of individual susceptibility.

The question of whether or not phenytoin affects the cognitive and motor abilities (so far, it appears it does not) of those who take it must be unequivocally answered using the battery of tests that was just developed and assembled by Captain Ahmed, for this specific purpose. And finally, as time and resources permit, it should be investigated to see if phenytoin's efficacy can be enhanced through its combination with another drug or drugs.

The testing of phenytoin's efficacy by outside agencies, such as the planned shuttle experimentation and the recent study at Edwards AFB, in concert with AFIT's research must continue and expand to provide testing under operational conditions. The information acquired under actual conditions needs to be compared to that of the laboratory to ensure the lab results are realistic and to add to the growing database of knowledge on the subject. The true test of phenytoin will be its ability to work in the field.

As for the use of topographical mappings in an attempt to identify, by frequency, amplitude, and location, what is happening in the brain (or at least on the cortical surface of the brain) during the onset and progression of motion sickness, again time and subjects are the answer. There are many difficult aspects to this study. Yes, it does appear that certain tendencies have been identified and it does appear that motion sickness affects the EEG signals (usually

increasing) of those experiencing it, but there are still
many unanswered questions. There is a continuous learning
curve that must be scaled when trying to identify sources of
artifact, the correct ground and reference to use, the
correct electrode locations, and what the system hardware
and software is doing.

This method of analysis can be a great asset, but it
will take more time to fully understand the Bio-logic
system. The data that are analyzed must be more artifact-
free and need to be more standardized in how they are
gathered, just as previously discussed for phenytoin.
Better documentation of trials is required. All pertinent
information including possible sources of artifact must be
recorded. This allows for some artifact identification and
may allow future data to be edited appropriately.

As the procedures become even more standardized and the
number of subjects increases, the data will become more
meaningful. The two trials of each subject should be
compared to one another as well as to a normative database.
Then the subjects should be compared to each other.

The methods of presentation and analysis also need to be
improved. Visual inspection has been adequate as a first-
cut attempt to coherently analyze this data, but other more
exact methods need to be developed. Perhaps some form of
statistical and/or frequency analysis (spectral possibly)

will be the answer. Presenting the results in a different manner may also help. Perhaps using longer "snapshots" (48 seconds, for example) would be advantageous. Different frequency regimes may also help. Presenting the data in movie form, either by recording it with a camcorder or by putting it on Silicon Graphics, may also be quite useful. This could be done for an entire trial or for selected segments.

Adjusting the sampling windows (currently 2 seconds) by offsetting the start of mapping of the same segment of data by 1 second could provide a clearer picture of what is really happening by providing an intermediate map. Figures 26 and 27 show how this could be done. The Figure 26 maps start at 00:00:46 and end at 00:01:09 for 23 seconds of data while the Figure 27 maps start at 00:00:45 and end at 00:01:09 for 24 seconds of data. So, to follow the maps correctly, start with the upper left-hand map of Figure 27, go to the upper left-hand map of Figure 26, then go to the top row, second from the left (on the right next to the last one from this set you looked at) of the Figure 27 maps, and so on until you finish in the lower right-hand corner of the Figure 26 maps. Together, the two sets of maps provide a fairly complete picture of what is happening. Of course, one second windows without the required offset or data manipulation would be better, but that may not be possible.
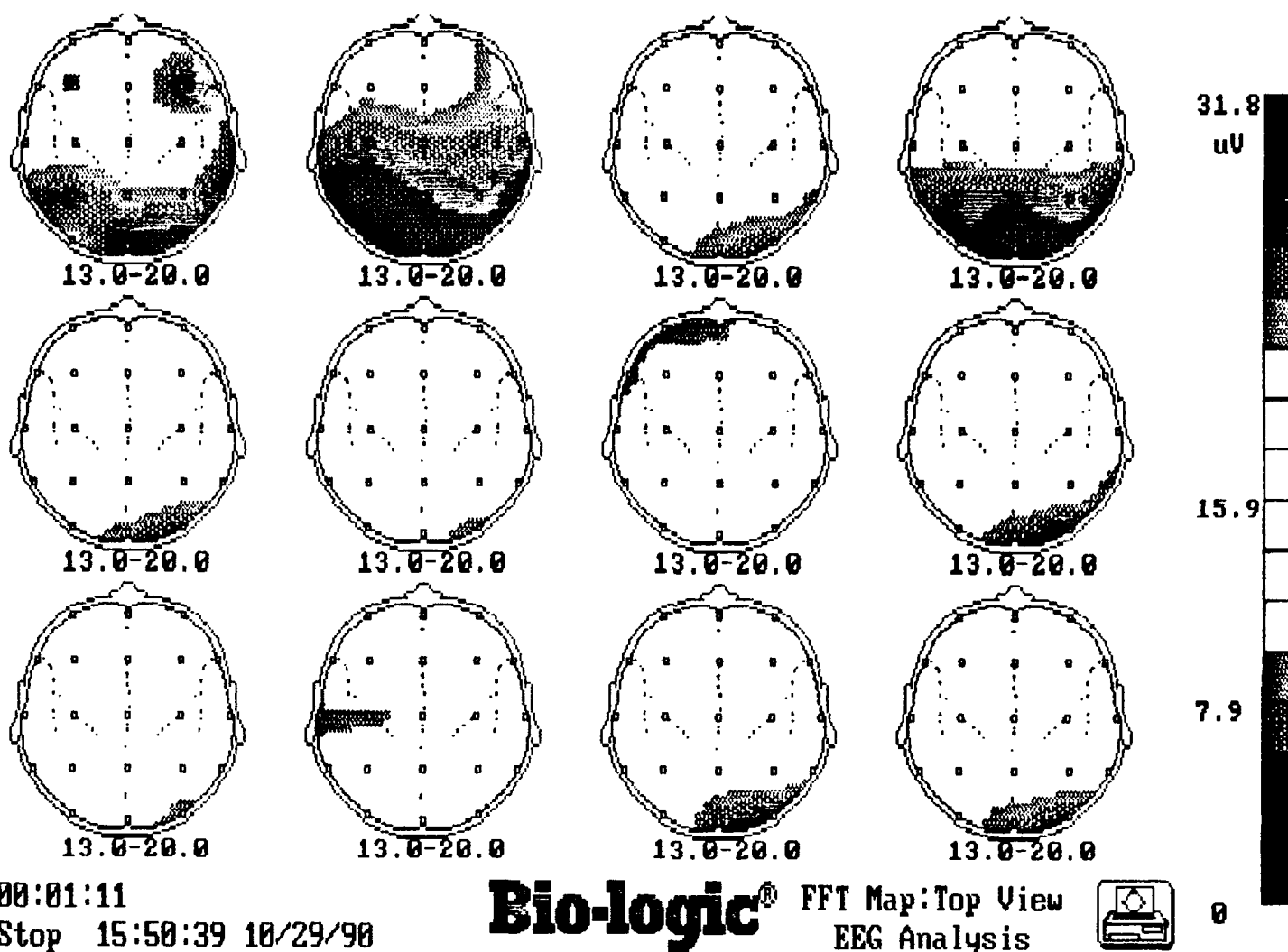
Figure 26 Offset Brain Maps Demonstrating One Second Window Capability (1 of 2)
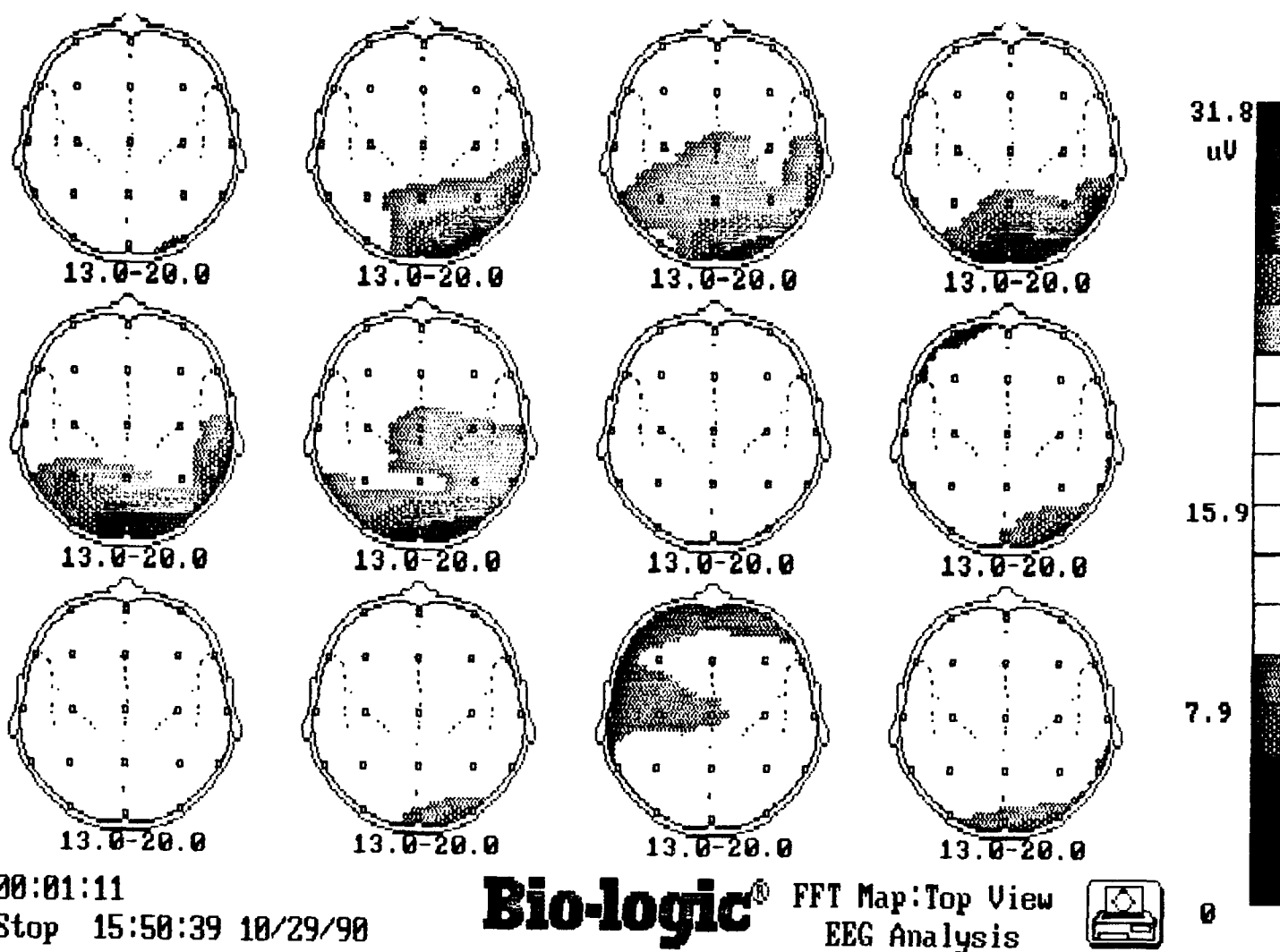
**Figure 27   Offset Brain Maps Demonstrating One Second
Window Capability (2 of 2)**

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Even better would be the capability to adjust the window to any length of time desired. A serious shortcoming of the Bio-logic system is its apparent inability to support a variable range of sampling window lengths. This is critical as EEG signals are not static and change more rapidly than just every two seconds. The correct window length may only be .5 seconds, but it is impossible to test to determine the optimal length at this time. Without the ability to better view those transitional periods that are omitted using two second windows, significant trends or events in the data may be overlooked or lost, and the interpretation of the data may be incorrect.

Perhaps the use of one of these methods of analysis and/or presentation will provide a definitive answer to the questions of whether there exists a propagation pattern or a point of origin in the brain for motion sickness.

And finally, the delta band (< 0.5 Hz in particular) must be extensively studied to determine if there is sufficient evidence to justify the hypothesis that the occurrence of motion sickness and its effect on the human electroencephalogram are similar to those of a partial seizure. The demonstration of this type of increase in activity in the delta band would be the first of its kind. The study of this possible correlation between motion

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sickness and epilepsy could have very important

ramifications in other aspects of medicine if successful.

Finally, this effort may not have answered all the

questions, but it certainly laid the foundation upon which

future successes in this area of research at AFIT may be

built.

Appendix A: 1990 Experimental Protocol

1. **Title:**   Evaluation of the Therapeutic
                                       Efficacy of Phenytoin in Motion
                                       Sickness.

2. **Principal Investigator:**   William Chelen, M.D.:
                                       255-5276; AFIT/ENG

    Associate Investigators: Matthew Kabrisky, Ph.D.:
                                       255-5276; AFIT/ENG

                                       Major Steven Rogers, Ph.D.:
                                       255-6027; AFIT/ENG

                                       Capt. Todd Banducci, B.S.:
                                       255-5276; AFIT/ENG

                                       1Lt. Nagin Ahmed, B.S.:
                                       255-5276; AFIT/ENG

3. **Date:** 21 Feb 1990   **Type:** Specific   **Renewal:** Yes

4. **Synopsis:**

Our recent experimental work on motion sickness character-
ization has revealed the frequent presence of electroencephalo-
graphic changes early in the onset of the syndrome. High
amplitude cortical potentials of this nature are usually only
seen in severe circumstances such as hypoxia, hypercarbia, or
drug induced seizure activity. These EEG changes in our motion
sick subjects suggested that motion sickness might be remedied
with a generalized neuronal stabilizing drug such as an
anticonvulsant.

This study is an attempt to quantify the efficacy of
phenytoin upon motion sickness, to determine minimum effective
doses of the agent and to establish dose response curves to
optimize treatment and minimize or eliminate side effects. (New
equipment, a computer controlled rotating motion simulator chair
was added in early 1989. This chair is a state of the art
rotation device currently employed in routine clinical
visual/vestibular examination and diagnosis.)

5. **Summary of Last Year's Experience:**

Through 1989, approximately 23 subjects participated in the
investigation of Dilantin's efficacy in motion sickness therapy.
In all of those tested with a therapeutic blood level
(approximately 10- 20 mcg./ml.), a significant increase to motion
tolerance was observed. An average improvement of 600 to 800%
was obtained. In three subjects, during the treatment trial, no
motion sickness symptoms were produced after more than an hour of
stimulation.

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Phenytoin serum level determinations have provided us with preliminary data that suggest that a serum level in the traditional anticonvulsant range is necessary for therapeutic efficacy in motion sickness as well.

The only occasion of adverse experience was that of a transient pruritic rash (in a volunteer with a history of multiple drug induced rashes). The experiment was terminated half way into the loading dose with a rapid and complete resolution of the rash.

AFIT/ENG Research Protocol

I. IDENTIFICATION

1. Title: Evaluation of the Therapeutic Efficacy of Phenytoin in Motion Sickness.

2. Date: 21 Feb 1990

3. Project/Task/Work Unit: N/A

4. Principal Investigator: William Chelen, M.D.; 255-5276; AFIT/ENG.

5. Associate Investigators: Matthew Kabrisky, Ph.D.; 255-5276; AFIT/ENG.

Steven Rogers, Ph. D; 255-6027; AFIT/ENG.

Todd Banducci, B.S.; 255-5276; AFIT/ENG.

Nagin Ahmed, B.S.; 255-5276; AFIT/ENG.

6. Medical Consultant: Colonel Donald Spoon, M.D.; USAF/MC.

II. RESEARCH BASIS

1. Objective

The purpose of this study is to determine the therapeutic value of the anticonvulsant agent, phenytoin (Dilantin*), in the prevention and treatment of motion sickness.

2. Relevance

All of the varied forms of motion sickness: airsickness, seasickness, and space-motion sickness (space adaptation syndrome)(12)(26) continue to be a problem without resolution. Costs and liabilities remain high, not just in economic terms, but in the compromise of comfort, safety, and even life when crew members are symptomatic (8)(21)(23).

Current therapies rely largely upon drug treatments: remedies only partly successful. The best agents, in combination, provide a 2 to 3 time increase in tolerance to motion, but have unacceptable side effects. Reactions such as blurred vision, dizziness, and lethargy are very common (8)(30) and obviate the use of effective agents in modern aviation. Due to these side effects and their effects upon alertness and performance, all antimotion sickness drugs currently in use are prohibited in all federal aviation and military operations except those in space.

3. Background

Current chemotherapeutic treatment regimens are based on the original empirical observation of efficacy of many varied agents with diverse biochemical target cells and organs. Agents within the drug classes of antihistiminic, anticholinergic, and sympathomimetic have been most extensively studied (18)(30). Each targets a specific subgroup of neuro-transmitters now known to be found in diverse but critical locations throughout the vestibular apparatus, brainstem, basal ganglia, and their interconnections.

Theory of the mechanism of action of the anticholinergics such as scopolamine is focused upon their ability to block inappropriate or excessive cholinergic activity (17)(31). Sympathomimetic agents are believed to act upon adrenergic or dopaminergic neurons which normally provide a balance or counterforce to the activity of cholinergic cells. A more direct action of the sympathomimetics is suggested by (19) where dopaminergic neuron activity inhibits acetylcholine release in the basal ganglia.

Our proposal to employ phenytoin is not based upon serendipitous observation of unexpected drug efficacy. It is founded upon two interrelated observations; a novel experimental "discovery", and a long recognized clinical neurological disorder. The first is the not infrequent presence of unusual electroencephalographic (EEG) changes in our current studies of acute motion sickness experimentation. These EEG changes consist of high voltage very low frequency oscillations in the delta to sub delta (0.2 to 0.3 Hertz) range (13). The second is the well defined clinical syndrome of autonomic and vegetative symptoms found in psychomotor (partial) seizures. This seizure disorder is very frequently characterized by visceral symptoms such as epigastric sensation, gastrointestinal hypermotility, plus

cardiovascular, respiratory, and other autonomic dysfunctions. All of these signs and symptoms are almost invariably found in the motion sickness syndrome (3)(8).

Phenytoin is primarily used for grand mal and partial seizure (a focal seizure type) prophylaxis, but it is also effective in controlling autonomic seizures (2)(16)(25).

If motion sickness is an analog of the simple partial seizure, as our evidence suggests, then an agent with efficacy in the latter disease would be expected to provide protection in the former.

Phenytoin acts diffusely upon the central nervous system in general to stabilize neuronal membranes (11). It tends to "stabilize the threshold against hyperexcitability caused by excessive stimulation". Phenytoin prevents the spread of seizure activity by blocking the transmission from an active focus. It also "reduces the maximal activity of brain stem centers" that initiate seizures (25). While phenytoin does act to normalize increased neuronal excitability, it has only limited ability to elevate normal threshold. Except in toxic doses, it does not interfere with normal cellular function.

At the dose level that we shall administer, the normal dose range, phenytoin is not a sedative (1)(11).

4. Experimental Plan

    A. Equipment and Facilities

    (1). All experimental test sessions and data
         collection will be conducted in the AFIT
         Engineering Building 640, room 242.

    (2). All experiments will consist of a test
         subject performing head movements in
         a rotating chair. A tape recorder
         directs the subjects through a sequence
         of random head movements every ten
         seconds.

    (3). Overall, the following equipment will be
         used:

         Equipment-subject interface:

         1. Rotating chair for eliciting the
            motion sickness response.
            (Neurokinetics model 8010 rotary
            chair system.)
         2. Chair speed control console.
         3. Electrodes:
            a. Meditronic Medical "Huggables"
               Infant Monitoring Electrodes.
            b. NDM silver/silver chloride electrodes.

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c. Subdermal EEG electrodes.

(Note: all sensors and electrodes connect
through 100K to 1 Meg ohm isolation
resistors to 12-volt battery powered
amplifiers and processing circuitry. The
data passes through slip rings to data
recording equipment.) (4)

4. Safety belt in the rotating chair.
5. An Astropulse 90 Blood Pressure Cuff
   to record arterial blood pressure.
6. Two pneumographs used to measure
   respiration (both abdominal and
   thoracic). The pneumographs are
   circumferential belts that employ
   strain gauges to detect respiration
   rate and depth changes.

   (Note: the pneumographs are electrically
   isolated from the subject.)

7. Two thermistors for measuring skin
   temperature.

   (Also electrically isolated from the subject.)

8. Two GSR electrodes for measuring
   skin conductance.
9. Two plethysmographs for measuring
   blood flow volume (pallor). They
   are photo transistors, resistors,
   and an LED mounted in an epoxy
   housing. One is attached to the
   index finger and the other to the
   subject's cheek. Both plethysmo-
   graphs are self-adhesive.
10. A phonosplanchnograph for a record
    of audible gastrointestinal
    mechanical activity (battery powered
    Intech Dif-Stet).
11. A contingency motion sickness bag
    of the type issued to Air Force
    aircrews and passengers.
12. An Ace elastic bandage and manual blood
    pressure cuff for pallor calibration.
13. Clinical Spirometer: Spirometrics model 2500.
14. Expired carbon dioxide monitor (Puritan
    -Bennett/Datex Instr. Corp. model 223).

Recording equipment:

1. Soltec model 8k26 16 channel strip chart recorder.
2. 2 Kyowa Dengyo RTP-610A 14 channel FM data recorders.
3. A Zenith 248 computer will be used for statistical data analysis and real time display and evaluation.

Clinical and Laboratory Evaluation

1. Motion sickness susceptibility test.
2. Personal and family medical history.
3. General physical examination.
4. Clinical vestibular, visual examinations.
5. Complete blood count (CBC).
6. Blood biochemistry screen (Chem 18 including liver function tests).
7. Blood cholesterol and lipids.
8. Chest X-Ray.
9. Urinalysis.
10. Electrocardiogram.
11. Phenytoin serum levels.
12. Written and interactive cognition and performance testing (X2).

Pharmacologic Agents.

1. Phenytoin (Dilantin*); maximum 200 milligram dose X 5 to 7 doses.

B. Method

The experimental design is one of a double blind, placebo controlled crossover type. Each suitable (see below) subject will on two different occasions at least one week apart, be administered either the active agent phenytoin, or a dextrose placebo. Each treatment will be administered in unmarked capsules in two lots of 5 to 7 capsules, lot A and lot B. Each subject will be issued a compliment of each lot. The identity of each lot, either phenytoin or placebo, will be known only to the principal investigator. The subject will randomly decide the order in which he will take a single lot prior to each of the two experimental sessions and not reveal until after both sessions what the order was.

All subjects will initially undergo a susceptibility trial to ascertain that each is within the normal range of motion sickness susceptibility and to provide a basis to select a rotational speed for the

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experiments. Subjects will then undergo a thorough
history and physical examination to exclude any acute
or chronic systemic illness. Once excellent health is
assured, a more detailed examination will follow. All
healthy subjects will undergo a complete blood count
(CBC), a general battery of blood biochemistry
(SMA-12/18), an electrocardiogram, blood lipids and
cholesterol, chest X-ray, urinalysis, visual acuity
test, vestibular evaluation and liver function studies.
Subjects will then take routine performance-cognition
tests to provide a baseline for later comparison after
treatment. After treatment administration, blood will
be drawn to measure phenytoin serum levels. Subjects
will then be retested for performance-cognition.

As much as possible, each experiment will be
standardized and follow an identical approach. Each
subject will receive both a written and oral briefing
describing what he can expect to experience during the
experiment, as well as have any questions answered.
Each subject will also receive a Subject Consent Form
to sign which further detail the experimental procedure
and experience.

Phenytoin or placebo treatment will begin the day
prior to the instrumented motion sickness induction
trial. Drug administration, 15 milligrams per kilogram
of subject's body weight (22), will begin at 14:00
hours with a 200 milligram dose, so that the volunteer
can be monitored for several hours that day for any
rare idiosyncratic reaction to the agent. The
following doses (also typically of 200 milligrams) will
follow at two hour intervals: at 17:00, 19:00, 21:00
and 23:00 hours. Subjects will be encouraged to take
all doses with meals to obviate any potential
gastrointestinal discomfort. The final dose of 200 to
400 milligrams will be scheduled for the next day at
08:00 hours with a prescribed breakfast. The
experimental procedure, with instrumentation
application, should begin by 12:00 hours that day and
the actual experimental rotation by 13:30 hours.

The experimental procedure will begin with a
review of the subject's experience with the course of
phenytoin administration and any side effects will be
noted. A standard physical examination will be
performed to determine each subject's physical
capability to participate in the experiment and to
determine any signs of drug related side effects. The
performance- cognition tests will then be administered
if no problems are noted.

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Instrumentation application and calibration will then procede with the pallor calibration using the elastic wrap and blood pressure cuff. The wrap is applied around the hand and wrist to blanch the region and a blood pressure cuff is inflated about the proximal portion of the wrap to 200 mm Hg. (5)(9)(10). The elastic is removed to permit the application of adhesive sensors to the hand to calibrate maximal pallor. Within a few minutes the cuff is deflated and a hyperemic or flush response is measured.

Areas of electrode placement are then vigorously scrubbed and adhesive silver-silver chloride surface and subdermal electrodes are then applied over the abdomen, trunk, and head, and the various cuffs, belts, straps, and sensors are attached.

The subject is then assisted into the motion simulator chair, and is restrained by a safety belt. He then breathes several breaths into a spirometer for respiratory volume calibration, and has his eyelids taped closed to minimize eye blink artifact and visual reference. A plastic nose piece with sampler tube is then taped in place just inside one nostril (for carbon dioxide sampling).

The experiment will then begin by rotating the chair at a rate determined by the previous susceptibility test. A velocity is chosen, typically 12 to 18 RPM, to enable an experimental session of a length of between 10 and 60 minutes. The subject's vital signs will be allowed to stabilize for approximately one minute before peforming head movements to permit the collection of the final segment of baseline or control period physiologic data.

Head movements will then be directed through an audio tape player according to a random sequence of tilts to the left, right, forward, and back upright. The head movements will normally continue until motion sickness symptoms are fully evolved. The subject's physiologic state will be constantly monitored, and the subject will be asked periodically for verbal reports on his condition. The experiment will continue until the full scale development of motion sickness symptoms or a maximum of 90 minutes.

Upon the subject's request to stop the experiment, the chair will be decelerated at a rate of approximately five RPM per minute to avoid any additional provocative stimulus. After the chair has come to a complete stop, the subject will remain seated

until all physiological indicators return to a state near the pretest values. All power will be removed from the chair to prevent accidental rotation. After the subject stabilizes, the eyelids will have their tape removed, and the subject will be assisted from the chair. All electrodes and sensors will be removed and the subject will be interviewed for any comments about the experiment. With the physician's approval, the subject will be released.

C. Subjects

Approximately twenty subjects will be required to complete the investigation. They will be male military and civilian members of the DOD. Total time required from each subject is estimated to be six to eight hours. An initial two to three hours will be devoted to questionnaire and clinical evaluation. An additional four to five hours will be required for the actual experimental sessions; with about a half hour for the susceptibility test, and two hours each for each experimental or control trial.

D. Reporting

All test data will be associated with the subject's name, but any publication of the data will not reveal the name or any other information about the subject. Data will not be available to anyone but the investigators. Upon request, subjects will be told about general results of the study, and will be shown the results of their particular test session.

E. Schedule

Experiments will begin upon protocol approval and all data should be collected by March, 1991.

F. Data analysis

The data will be analyzed by a variety of statistical means including t-tests, analysis of variance (ANOVA), spectral analysis, and brain mapping (Biologic Systems Corp).

III. Medical Risks, Safety Precautions, and Measures

1. Subjects.

Prior to an in-depth medical evaluation, all subjects will be tested for normal motion sickness susceptibility and

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experimental suitability in an uninstrumented trial run. This
abbreviated experiment will resemble a normal experiment in terms
of rotation and head movements to assure a normal tolerance and
response to coriolis stimulation.

All subjects of normal susceptibility will then proceed
through a sequence of testing; beginning with a motion and
symptom experience questionaire. A personal and family medical
history form will then be administered to identify familial or
genetic disorders and evidence of chronic and systemic disease.

Subjects will then be thoroughly evaluated clinically to
ensure absence of systemic disease of the hematologic,
cardiovascular, renal and gastrointestinal (hepatic), systems
through blood and urine analysis and with an electrocardiogram
and chest X-ray.

Normalcy of the visual and vestibular organs will be
ascertained with the clinical tests referred to in section 4c.

A pre-experiment physical exam will be performed to verify
that subjects are free from any significant treatment related
side effects. A pre-experiment blood sample will also be drawn
to quantify the serum level of phenytoin.

2. Risks.

A. Equipment

Risk related to equipment, instrumentation, and
calibration is minimal as detailed and approved in
protocol 86-13--20 of July, 1987. The motion simulator
is a modern clinical diagnostic system and been safely
employed for years ⱱn real world patients.

Virtually all nstrumentation is battery powered
and in addition is either electrically insulated from
the subject or connected through isolation resistors of
a minimum of 100,000 ohms (4)(29).

The calibration procedure with an elastic wrap is
of minimal risk and has also been so approved.

B. Dilantin* (Phenytoin)

Use and administration of phenytoin has a 50 year
history and a favorable record of safety. It is the
primary drug of choice for the treatment of most types
of seizures largely because of extensive clinical
experience.

Most side effects are dose related and are seen
with extra-therapeutic levels, serum levels exceeding
20 to 25 micrograms per milliliter (11)(27). Blood
levels in the 20's are associated with the readily
identified signs and symptoms of nystagmus and
diplopia.

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Much higher levels, greater than 30 micrograms/milliliter, lead to ataxia. Dysarthria and lethargy are seen at serum levels of greater than 40 micrograms per milliliter. These toxic levels are virtually always a result of chronic administration, or chronic administration combined with a stressor that reduces the normal rate of metabolism of the drug.

The occasional side effect of nausea or related gastrointestinal symptoms may be prevented by administering the drug with meals.

Adverse reactions to phenytoin, as with most drugs, either prescription or the commonly available types generally recognized as safe, are usually seen only with long term administration. Most organ systems can manifest adverse reactions during chronic administration but gingival hyperplasia is the most common.

The technique of treatment we shall be using, with the administration of a loading dose (in divided portions over a day), should provide virtually no possibility of producing the adverse reactions ascribed to long term administration. This loading dose, of 15 milligrams per kilogram of body weight, should also be incapable of producing serum levels of greater than 20 micrograms per milliliter and thus be unable to induce the dose related side effects previously mentioned.

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2. **Current PositionTitle:** Professor of Electrical
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   Location: Air Force Institute of Technology/WSU-SOM.
   WPAFB, Ohio.

3. **Education:**

   B.S., Electrical Engineering, Carnegie-Mellon Univ.,
   Pittsburgh, PA. 1971.
   B.S., Biology, University of Pittsburgh,
   Pittsburgh, PA. 1973.
   M.D., Temple University School of Medicine,
   Philadelphia, PA. 1979.

4. **Relevant Experience:**

   1987-1990: CONTRACTOR-Aerospace Medical Research
   and Teaching. AAMRL/AFIT Dept. of
   Electrical Engineering.
   1985-1987: SENIOR RESEARCH ASSOCIATE-National
   Research Council/AFAMRL/AFIT.
   1986-1987: CLINICAL INSTRUCTOR-Wright State
   University Department of Community
   Medicine.
   1983-1985: RESIDENCY IN AEROSPACE MEDICINE-
   Wright State University Department
   of Community Medicine.
   1984-1986: PHYSICIAN-Wright State University/FAWCAC.
   1983-1985: EMERGENCY ROOM PHYSICIAN-Independent
   Contractor/Southwestern Ohio.
   1982-1983: GENERAL MEDICAL PRACTICE-Washington, DC.
   1982-1983: MEDICAL DIRECTOR-Consumer Medical
   Services-Manna Corp, Arlington, VA.
   1979-1981: RESIDENCY IN ANESTHESIOLOGY/CRITICAL CARE
   MEDICINE-Georgetown University Hospital,
   Washington, DC.
   1979: National Aeronautic and Space
   Administration-Johnson Space Center,
   Houston, TX.

5. **Licensure:** Doctor of Medicine-Ohio. 1983.
   Medicine and Surgery-D.C. 1980.
   Diplomate-National Board of Medical
   Examiners. 1980.

PROTOCOL CURRICULUM VITAE

1. **Name:** Matthew Kabrisky, Ph. D.
   Grade of Rank: AD-24.

2. **Current Position Title:** Professor of Electrical
   Engineering.

   Location: Air Force Institute of Technology,
   WPAFB, Ohio.

3. **Education:**

   B. S., Electrical Engineering, Polytechnic Institute
                                  of Brooklyn, 1951.
   M. S., Electrical Engineering, Polytechnic Institute
                                  of Brooklyn, 1952.
   Ph. D., Electrical Engineering, University of
                                  Illinois, 1964.

4. **Member of the Series of Biomedical Engineering**
   Research Teams with AMRL since 1964.

5. **Licensure:** N/A.

PROTOCOL CURRICULUM VITAE

1. Name: Steven K. Rogers, Ph. D.
   Rank: Major, USAF

2. Current Position Title: Associate Professor of
   Electrical Engineering

   Location: Wright-Patterson Air Force Base, Ohio.

3. Education:

   B.S., Electrical Engineering, University of
   Colorado, 1978.

   B.S., Computer Science, University of Colorado,
   1978.

   M.S., Electrical Engineering, Air Force Institute of
   Technology, 1981.

   Ph. D., Electrical Engineering, University of
   Colorado, 1984.

4. Relevant Experience:

   Member of the Biomedical Research Team since 1984.

   Authored over twenty papers in optical information
   processing, stochastic estimation and control,
   pattern recognition, artificial intelligence,
   command-control-communications, optical information
   processing, and modeling of the central nervous
   system.

   Coauthor of: Defense Applications of Pattern
                  Recognition

                  Mathematical Modeling of the Central
                  Nervous System with Applications to
                  Neuromines.

5. Licensure: N/A

PROTOCOL CURRICULM VITAE

1. **Name:** Todd Banducci
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3. **Education:**

   B. S., Economics, U. S. Air Force Academy, Colorado
   Springs, Colorado, 1985.

4. **Relevant Experience:**

   1990:   Master's Degree thesis work at AFIT.

   1987-1989: Executive Officer, 5th Satellite Control
                     Squadron, Fairchild AFB, Washington.

   1985-1987: Satellite Operations Crew Commander, 5th
                     Satellite Control Squadron, Fairchild AFB,
                     Washington.

5. **Licensure:** N/A

PROTOCOL CURRICULUM VITAE

1. **Name:** Nagin Ahmed
   Rank: 1Lt., USAF

2. **Current Position Title:** Student, Air Force
   Institute of Technology, School of Engineering,

3. **Education:**

   B. S., Operations Research and Industrial Engineering,
   Cornell Univ., 1986.

   B. A., Experimental Psychology, Cornell Univ., 1986.

4. **Relevant Experience:**

   1990:   Master's degree thesis work at AFIT.

   1986-1989:   Training Systems Engineer, Directorate
                of Support Systems Engineering,
                Aeronautical Systems Division, WPAFB,
                Ohio.

5. **Licensure:** N/A

Subject Consent Form

Evaluation of the Terapeutic Efficacy
of Dilantin in Motion Sickness

1. You are invited to participate in an investigation of the
value of the anticonvulsant drug Dilantin (generically known as
phenytoin) in the prevention and treatment of motion sickness.
Our prior research has suggested that motion sickness is related
to a form of seizure disorder and should benefit form treatment
with a drug that has long been known to be effective in
preventing seizures.

The time required for all phases of this experiment is estimated
to be from 6 to 8 hours. Initially, the written questionnaires,
computerized performance testing, and laboratory evaluation is
expected to require 2 to 3 hours. Each actual experiment is
expected to average 2 to 3 hours.

2. The experimental procedure will consist first of a non-
instrumented rotating chair susceptibility trial run of several
minutes in duration to establish your normal susceptibility to
motion sickness. The next phase will include a preliminary
detailed questionnaire, medical history, and physical examination
with several routine blood tests and hospital laboratory
evaluations. Further testing both before and after treatment
administration will involve and automated physical performance
evaluation and cognition testing so that we can document that
treatment entails no appreciable side effects.

During the experiments we will be monitoring multiple physiologic
parameters with sensors (adhesive and subdermal electrodes, bands
and straps) attached to your chest, abdomen, arms, hands, and
head in order to evaluate your heart, lungs, blood pressure and
flow, stomach and intestines, eye movement, and brain waves.

The actual experiment will consist of two procedures on two
separate days about one to two weeks apart. The day before the
first procedure you will be issued two separate containers, A and
B, of treatment agents. Choose one container of capsules for the
first procedure and the other container for the second procedure.
Record the order in a secure place. Only after the conclusion of
the second procedure, when the Principal Investigator requests,
should you reveal your chosen sequence.

Initial _____

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The motion sickness induction phase of the experiment will involve your sitting instrumented in a rotating chair. A tape player will direct a sequence of head tilts for to perform. You must perform every head movement that is directed, until you decide to stop. Otherwise, please keep yourself (especially your hands and arms) as still as possible in order to maintain all the sensors in place. You will be periodically asked to report your symptoms and to rate them on a scale of from 1 (normal) to 10 (about to vomit). Report any and all symptoms you experience. These symptoms might include dizziness, spinning, disorientation, tingling, tiredness, warmth, cold, sweating, light-headedness, queasiness, salivation, dry or acid mouth, nausea, stomachache, headache, anxiety, apathy, etc. The end point of the experiments requires your reaching a frank state of motion sickness. You are in control of the stimuli that elicits the symptoms, the voluntary head motions. Once you cease the head motions, your symptoms will dissipate in a few minutes. Do not resist any symptoms, as this may influence the accuracy of our data.

3. Dilantin has a 50 year history of efficacy and a favorable record of safety. Most side effects associated with its use occur with long term continued administration. These include skin rashes and other forms of eruptions and dermatitis. The blood forming cells and lymph glands are occasionally affected. The connective tissues, lips, face, and gums can show coarsening with long term use. The nervous system can display sensory disturbances with long term Dilantin treatment. Rarely, most organ systems, the liver, blood vessels, etc., can be damaged as is the case with most drugs available over the counter or prescribed. The side effects seen with short term treatment include gastrointestinal disturbances and several nervous system impairments; these side effects are usually dose related, effects we do not expect due to the limited dose we shall administer over only one day.

Naturally, by virtue of the nature of this experiment which involves the induction of motion sickness, a degree of discomfort is anticipated for several minutes during each experimental session. These symptoms and their onset are under your control and quickly disappear when head motions are terminated.

4. Motion sickness: airsickness and seasickness continue to be a significant problem for both civilian and military populations. Not just comfort, but crew efficiency and safety are at stake during severe motion stimulation. Most recently, with frequent missions on the Space Shuttle, space motion sickness has taken a heavy toll. Over half of those (even with the best traditional treatment available) who have flown have been sick for up to several days. This investigation is an attempt to identify a new treatment that is both more effective than current agents and devoid of the side effects that impair performance and alertness.

Initial _____

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5. The alternative use of experimentally induced laboratory based, rather than real world motion stimulation, is necessary to provide a controlled repeatable stimulus and environment for measurement and study.

If you have any additional questions regarding this study or your participation, please contact Dr. William Chelen at 255-5276 or 433-6666.

6. I,_____, am participating because I want to. The decision to participate in this research study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program.

_____ has adequately answered any and all questions I have asked about this study, my participation, and the procedures involved. I understand that the Principal Investigator or his designee will be available to answer any questions concerning procedurres throughout this study. I understand that if significant new findings develop during the course of this research which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlements. I also understand that the Medical Consultant for this study may terminate my participation in this study if he feels this to be in my best interest. I may be required to undergo certain further examinations, if in the opinion of the Medical Consultant, such examinations are necessary for my health or well being.

I have considered and accept the unlikely but theoretical possibility as follows:

(1) If physical exams and or monitoring of physiological parameters related to this experiment are conducted, it is possible for an unknown physical defect to come to light which might result in disqualification from flight or other special duty.

(2) If physical injury were to occur it, could result in physical disqualification from flight or other special duty.

I understand that my entitlement to medical care or compensation in the event of injury are governed by federal laws and regulations, and that if I desire further information I may contact the Principal Investigator.

I understand that I will not be paid for my participation in this experiment.

Initial _____

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I understand that my participation in this study may be photographed, filmed, or audio/videotaped. I consent to the use of these media for training purposes and understand that any release of records of my participation in this study may only be disclosed according to federal law, including the Federal Privacy Act, 55 U.S.C. 552a, and its implementing regulations. This means personal information will not be released to an unauthorized source without my permission.

I FULLY UNDERSTAND THAT I AM MAKING A DECISION WHETHER OR NOT TO PARTICIPATE. MY SIGNATURE INDICATES THAT I HAVE DECIDED TO PARTICIPATE HAVING READ THE INFORMATION PROVIDED ABOVE.

Volunteer signature and SSAN _____ Date _____

Witness signature _____ Date _____

Appendix B: AFIT Motion Sickness Questionnaire

AFIT Motion Sickness Laboratory

Motion Sickness Questionnaire

NAME:_____ DATE:_____

RANK:_____ AGE:_____ SEX:_____

ADDRESS:_____

WEIGHT:_____ HEIGHT:_____

This questionnaire is designed to find out:

       (a). how susceptible to motion sickness you are, and
       (b). what types of motion are most provocative to you.

Section A is concerned with childhood (prior to age 12)

      experiences of motion sickness.

Section B is concerned with your experiences of motion

      sickness over the past 10 years.

Section C is concerned with your present susceptibility to

      motion sickness.

Please read and follow carefully the instructions for
each question. The answers are important for evaluating this
experiment. This information will be kept in the strictest
confidence. Thank you for your help.

Section A

All the questions in this section refer to your childhood experiences of motion sickness, that is, before age 12. We understand you may not remember this very well; just do your best.

	CARS	BUSSES	TRAINS	AIRPLANES	BOATS	SHIPS.	PLAYGROUND EQUIPMENT.	AMUSEMENT	PARK RIDES
(1) Indicate approximately how often you rode on each type (before age 12) by using the following: 0 = no experience 1 = less than 5 trips ' = between 5 and 10 3 = more than 10									
Considering only those types of transport that you have experience with, answer the two questions below. use the following letters to indicate your response: N=Never; R=Rarely; S=Sometimes; F=Frequently; A=Always									
(2) How often did feel sick while travelling (i.e. queasy or nausea)?									
(3) How often were you actively sick, (i.e. vomiting)?									

Section B

This section is concerned solely with your experiences of motion sickness over approximately the last 10 years.

	CARS	BUSSES	TRAINS	AIRPLANES	BOATS	SHIPS	PLAYGROUND	EQUIPMENT	AMUSEMENT	PARK RIDES
(1) Indicate approximately how often you rode on each type (over the last 10 years) by using the following										
0 = no experience 1 = less than 5 trips 2 = between 5 and 10 3 = more than 10										
Considering only those types of transport that you have experience with, answer the two questions below. use the following letters to indicate your response: N=Never; R=Rarely; S=Sometimes; F=Frequently; A=Always										
(2) How often did feel sick while travelling (i.e. queasy or nausea)?										
(3) How often were you actively sick, (i.e. vomiting)?										

Section C

This section is concerned with your present susceptibility to motion sickness. If a question does not apply to you, enter "None" or "NA".

(1). What is your current flying status? (Pilot, Navigator, UPT/UNT, etc)._____.

(2). what operational or fully qualified flying experience have you had? (Plane, Hours, Crew position, Command).

_____

(3). I (have have not) been treated for motion sickness. My treatment consisted of _____

_____

for _____ months, at _____

by _____, which (did did not) help.

Treatment did not help because _____

_____

(4). I currently consider myself:

    (a). mildly
    (b). Moderately
    (c). Severely
    (d). Not at all . . . . susceptible to motion sickness.

(5). When the opportunity arises, I:

    (a). Almost never
    (b). Sometimes
    (c). Almost always . . . . ride carnival rides

(6). I would describe my current experiences with motion sickness as:

    (a). Totally disabling
    (b). Occasionally disabling
    (c). Debilitating but not disabling
    (d). Only bothersome
    (e). Not affected

(7). When I have been airsick on a flight, I:

    (a). Almost always
    (b). Sometimes
    (c). Almost never . . . . have trouble deplaning.
    (d). No airsickness experienced.

(8). Other members of my family are susceptible to motion sickness.

    (a). Do not know
    (b). No
    (c). Yes (elaborate) _____

(9). The following symptoms usually accompany my experience of motion sickness: (circle all that apply)

Nausea	Dizziness
Vomiting	Disorientation
Sweatiness	Desire to be left alone
Gassiness	Yawning
Coldness	Difficult concentration
Churning stomach	Tingling hands and feet
Reluctance for physical or mental work	Objects/sounds seem distant
Headache	Chest pains
Fatigue or drowsiness	Distractibility
Faintness	Thick headedness
Blurred/tunnel vision	Spaced out
Other (elaborate) _____	

(10). I have found the following situations and their
      accompanying body motion sensations to be pleasant (P)
      or unpleasant (U) for the most part: (Indicate any not
      experienced by "NA").

      _____Fast elevator rides   _____Gymnastics
      _____Escalator rides   _____Inverted flight
      _____Dancing   _____Mountain driving
      _____Inflight positive Gs   _____Hammocks
      _____Inflight negative Gs   _____Tipsy from drinking
      _____Skiing (water/snow)   _____Jogging
      _____Train/subway rides   _____Skating
      _____Swings   _____Motorcycle riding
      _____Merry-go-rounds   _____Glider/small planes
      _____Roller coasters   _____Boating
      _____Other midway rides   _____Low level flight
      _____Stationary spinning   _____Ships
      _____Other (elaborate) _____

(11). Have you ever been eliminated from a flying training
      program?

      _____No
      _____Yes (elaborate) _____

(12). Are you currently taking any medications (including
      aspirin and antihistamines)?

      _____No
      _____Yes (specify) _____
      How long? _____

(13). Have you had any alcohol in the last 24 hours?

      _____No
      _____Yes

(14). How long ago was your last meal? _____Hours

(15). Have you had any unusual motion stimuli in the past 24
      hours (aircraft rides, carnival rides, etc?)

      _____No
      _____Yes (specify) _____

(16). Have you had any vision problems recently (general
      worsening, change in prescription of corrective lenses,
      etc.)?

      _____No
      _____Yes (specify) _____

(17). Have you had any stomach upsets in the past month?

_____No
_____Yes

(18). What is your current assessment of your health?

_____Excellent _____Good _____Fair _____Poor

(19). What can you add that might be beneficial to this study or that would improve this questionnaire?

Appendix C: Patient Questionnaire

PATIENT QUESTIONNAIRE

PATIENT'S NAME _____ BIRTH DATE _____ SEX _____ S. M. W. D.

ADDRESS _____ TEL. NO. _____

INSURANCE _____ REFERRED BY _____ OCCUPATION _____

INSTRUCTIONS: PUT ☑ IN THOSE BOXES APPLICABLE TO YOU AND IN THE "YES" OR "NO" SPACE. IF LINES ARE PROVIDED WRITE IN YOUR ANSWER.

FAMILY HISTORY

	FATHER	MOTHER	BROTHER				SISTER				SPOUSE	CHILDREN					
			1	2	3	4	1	2	3	4		1	2	3	4	5	6
AGE (IF LIVING)																	
HEALTH (G) GOOD (B) BAD																	
CANCER																	
TUBERCULOSIS																	
DIABETES																	
HEART TROUBLE																	
HIGH BLOOD PRESSURE																	
STROKE																	
EPILEPSY																	
NERVOUS BREAKDOWN																	
ASTHMA, HIVES, HAYFEVER																	
BLOOD DISEASE																	
AGE (AT DEATH)																	
CAUSE OF DEATH																	

PERSONAL HISTORY

HAVE YOU EVER HAD ...	NO	YES	HAVE YOU EVER HAD ...	NO	YES	HAVE YOU EVER HAD ...	NO	YES
☐ SCARLET FEVER ☐ SCARLATINA			☐ GONORRHEA ☐ SYPHILIS			ANY ☐ BROKEN ☐ CRACKED BONES		
DIPHTHERIA			ANEMIA			RECURRENT DISLOCATIONS		
SMALLPOX			JAUNDICE			☐ CONCUSSION ☐ HEAD INJURY		
PNEUMONIA			EPILEPSY			EVER BEEN KNOCKED UNCONSCIOUS		
PLEURISY			MIGRAINE HEADACHES			☐ FOOD ☐ CHEMICAL ☐ DRUG POISONING		
UNDULANT FEVER			TUBERCULOSIS			EXPLAIN		
☐ RHEUMATIC FEVER ☐ HEART DISEASE			DIABETES					
ST. VITUS DANCE			CANCER					
☐ ARTHRITIS ☐ RHEUMATISM			☐ HIGH ☐ LOW BLOOD PRESSURE			ANY OTHER DISEASE		
ANY ☐ BONE ☐ JOINT DISEASE			NERVOUS BREAKDOWN			EXPLAIN		
☐ NEURITIS ☐ NEURALGIA			☐ HAY FEVER ☐ ASTHMA					
☐ BURSITIS ☐ SCIATICA ☐ LUMBAGO			☐ HIVES ☐ ECZEMA					
☐ POLIO ☐ MENINGITIS			FREQUENT ☐ COLDS ☐ SORE THROAT			WEIGHT: NOW ONE YR. AGO		
BRIGHT'S DISEASE			FREQUENT ☐ INFECTIONS ☐ BOILS			MAXIMUM WHEN		

ALLERGIES

ARE YOU ALLERGIC TO ...	NO	YES	ARE YOU ALLERGIC TO ...	NO	YES	ARE YOU ALLERGIC TO ...	NO	YES
☐ PENICILLIN ☐ SULFA DRUGS			ANY OTHER DRUGS			ANY FOODS		
☐ ASPIRIN ☐ CODEINE ☐ MORPHINE			EXPLAIN			EXPLAIN		
☐ MYCINS ☐ OTHER ANTIBIOTICS								
☐ TETANUS ☐ ANTITOXIN ☐ SERUMS			ADHESIVE TAPE			☐ NAIL POLISH ☐ OTHER COSMETICS		

SURGERY

HAVE YOU HAD REMOVED ...	NO	YES	HAVE YOU HAD REMOVED ...	NO	YES	HAVE YOU ...	NO	YES
TONSILS			☐ OVARY ☐ OVARIES			HAD HERNIA REPAIRED		
APPENDIX			HEMORRHOIDS			HAD ANY OTHER OPERATIONS		
GALL BLADDER			EVER HAVE A TRANSFUSION (...)			BEEN HOSPITALIZED FOR ANY ILLNESS		
UTERUS			☐ BLOOD ☐ PLASMA			EXPLAIN		

X-RAYS

EVER HAVE X-RAYS OF ...	NO	YES	DATE	DISEASE PRESENT
CHEST				
☐ STOMACH ☐ COLON				
GALL BLADDER				
EXTREMITIES				
BACK				
OTHER				

FORM NO. 400

HISTACOUNT CORPORATION, MELVILLE, N. Y. 11746

SYSTEMS

DO YOU NOW HAVE OR HAVE YOU EVER HAD...	NO	YES	DO YOU NOW HAVE OR HAVE YOU EVER HAD...	NO	YES
ANY [ ]EYE DISEASE [ ]EYE INJURY [ ]IMPAIRED SIGHT			KIDNEY [ ]DISEASE [ ]STONES		
ANY [ ]EAR DISEASE [ ]EAR INJURY [ ]IMPAIRED HEARING			BLADDER DISEASE		
ANY TROUBLE WITH [ ]NOSE [ ]SINUSES [ ]MOUTH [ ]THROAT			BLOOD IN URINE		
FAINTING SPELLS			[ ]ALBUMIN [ ]SUGAR [ ]PUS [ ]ETC. IN URINE		
CONVULSIONS			DIFFICULTY IN URINATION		
PARALYSIS			NARROWED URINARY STREAM		
DIZZINESS			ABNORMAL THIRST		
HEADACHES: [ ]FREQUENT [ ]SEVERE			PROSTATE TROUBLE		
ENLARGED GLANDS			[ ]STOMACH TROUBLE [ ]ULCER		
THYROID: [ ]OVERACTIVE [ ]UNDERACTIVE [ ]ENLARGED			INDIGESTION		
ENLARGED GOITER			[ ]GAS [ ]BELCHING		
SKIN DISEASE			APPENDICITIS		
COUGH: [ ]FREQUENT [ ]CHRONIC			[ ]LIVER DISEASE [ ]GALL BLADDER DISEASE		
[ ]CHEST PAIN [ ]ANGINA PECTORIS			[ ]COLITIS [ ]OTHER BOWEL DISEASE		
SPITTING UP BLOOD			[ ]HEMORRHOIDS [ ]RECTAL BLEEDING		
NIGHT SWEATS			BLACK TARRY STOOLS		
SHORTNESS OF BREATH [ ]EXERTION [ ]AT NIGHT			[ ]CONSTIPATION [ ]DIARRHEA		
[ ]PALPITATION [ ]FLUTTERING HEART			[ ]PARASITES [ ]WORMS		
SWELLING OF [ ]HANDS [ ]FEET [ ]ANKLES			[ ]ANY CHANGE IN APPETITE [ ]EATING HABITS		
VARICOSE VEINS			[ ]ANY CHANGE IN BOWEL ACTION [ ]STOOLS		
EXTREME [ ]TIREDNESS [ ]WEAKNESS			EXPLAIN		

IMMUNIZATION - EKG

HAVE YOU HAD...	NO	YES	HAVE YOU HAD...	NO	YES
SMALLPOX VACCINATION (WITHIN LAST 7 YEARS)			POLIO SHOTS (WITHIN LAST 2 YEARS)		
TETANUS SHOT (NOT ANTITOXIN)			AN ELECTROCARDIOGRAM WHEN		

HABITS

DO YOU...	NO	YES	DO YOU USE...	NEVER	OCC.	FREQ.	DAILY
EXERCISE ADEQUATELY			LAXATIVES				
HOW?			VITAMINS				
AWAKEN RESTED			SEDATIVES				
SLEEP WELL			TRANQUILIZERS				
AVERAGE 8 HOURS SLEEP (PER NIGHT)			SLEEPING PILLS, ETC.				
HAVE REGULAR BOWEL MOVEMENTS			ASPIRINS, ETC.				
SEX - ENTIRELY SATISFACTORY			CORTISONE				
LIKE YOUR WORK (HOURS PER DAY) [ ]INDOORS [ ]OUTDOORS			ALCOHOLIC BEVERAGE				
WATCH TELEVISION (HOURS PER DAY)			COFFEE (CUPS PER DAY)				
READ (HOURS PER DAY)			TOBACCO:[ ]CIGARETTES (PKS PER DAY)				
HAVE A VACATION (WEEKS PER YEAR)			[ ]CIGARS [ ]PIPE [ ]CHEWING TOBACCO				
HAVE YOU EVER BEEN TREATED FOR ALCOHOLISM			[ ]SNUFF				
HAVE YOU EVER BEEN TREATED FOR DRUG ABUSE			APPETITE DEPRESSANTS				
RECREATION: DO YOU PARTICIPATE IN SPORTS OR HAVE			THYROID MEDICATION: [ ]NO [ ]YES, IN PAST [ ]NONE NOW NOW ON GR. DAILY				
HOBBIES WHICH GIVE YOU RELAXATION AT			HAVE YOU EVER TAKEN...				
LEAST 3 HOURS A WEEK.			[ ]INSULIN [ ]TABLETS FOR DIABETES [ ]HORMONE SHOTS [ ]TABLETS [ ]NO				

WOMEN ONLY

MENSTRUAL HISTORY...				NO	YES
AGE AT ONSET		ARE YOU REGULAR [ ]HEAVY [ ]MEDIUM [ ]LIGHT			
USUAL DURATION OF PERIOD DAYS		DO YOU HAVE [ ]TENSION [ ]DEPRESSION BEFORE PERIOD			
CYCLE (START TO START) DAYS		DO YOU HAVE [ ]CRAMPS [ ]PAIN WITH PERIOD			
DATE OF LAST PERIOD		DO YOU HAVE HOT FLASHES			
PREGNANCIES...		NO	YES	NO	YES
CHILDREN BORN ALIVE (HOW MANY)		STILL BORN (HOW MANY)			
CESAREAN SECTIONS (HOW MANY)		MISCARRIAGES (HOW MANY)			
PREMATURES (HOW MANY)		ANY COMPLICATIONS			

EMOTIONS

ARE YOU OFTEN...	NO	YES	ARE YOU OFTEN...	NO	YES
DEPRESSED			JUMPY		
ANXIOUS			JITTERY		
IRRITABLE			IS CONCENTRATION DIFFICULT		

165

Appendix D: Topographic Brain Maps

Phenytoin Trial
Subject #5
Frequency 3.0 to 8.0 Hz
Baseline - Sitting at Rest

166

Phenytoin Trial
Subject #5
Frequency 3.0 to 8.0 Hz
Baseline - Spinning Prior to First HM

Bio-logic® FFT Map:Top View EEG Analysis

00:02:44

Phenytoin Trial
Subject #5
Frequency 3.0 to 8.0 Hz
Symptom Level 2-3

31.8
uV

15.9

7.9

00:00:26

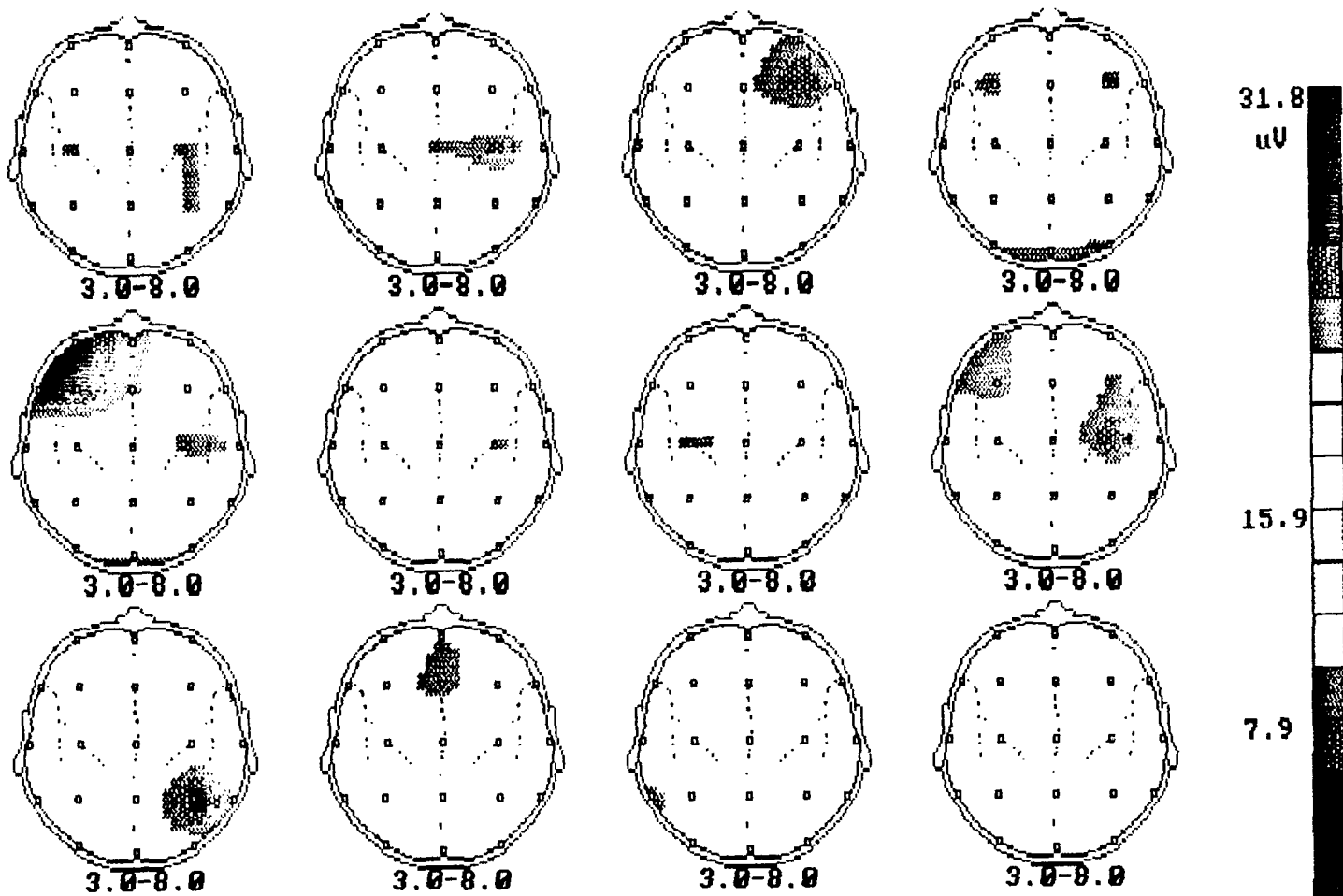**Bio-logic**® FFT Map:Top View
EEG Analysis

0

Phenytoin Trial
Subject #5
Frequency 3.0 to 8.0 Hz
Symptom Level 5

00:01:11
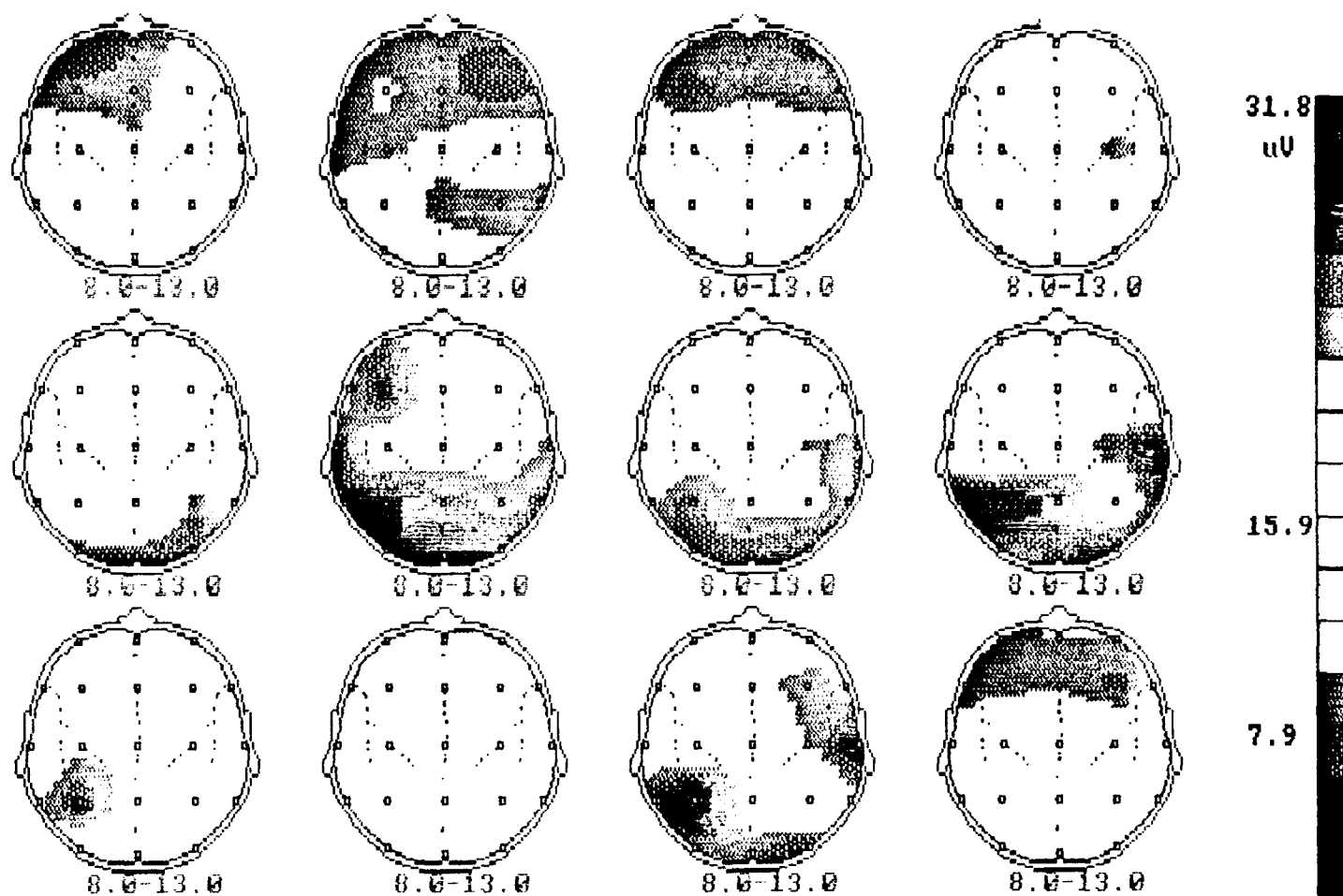Stop 15:50:39 10/29/90

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

169

00:00:41   **Bio-logic**® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Phenytoin Trial
Subject #5
Frequency 3.0 to 8.0 Hz
Symptom Level 9-10

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0
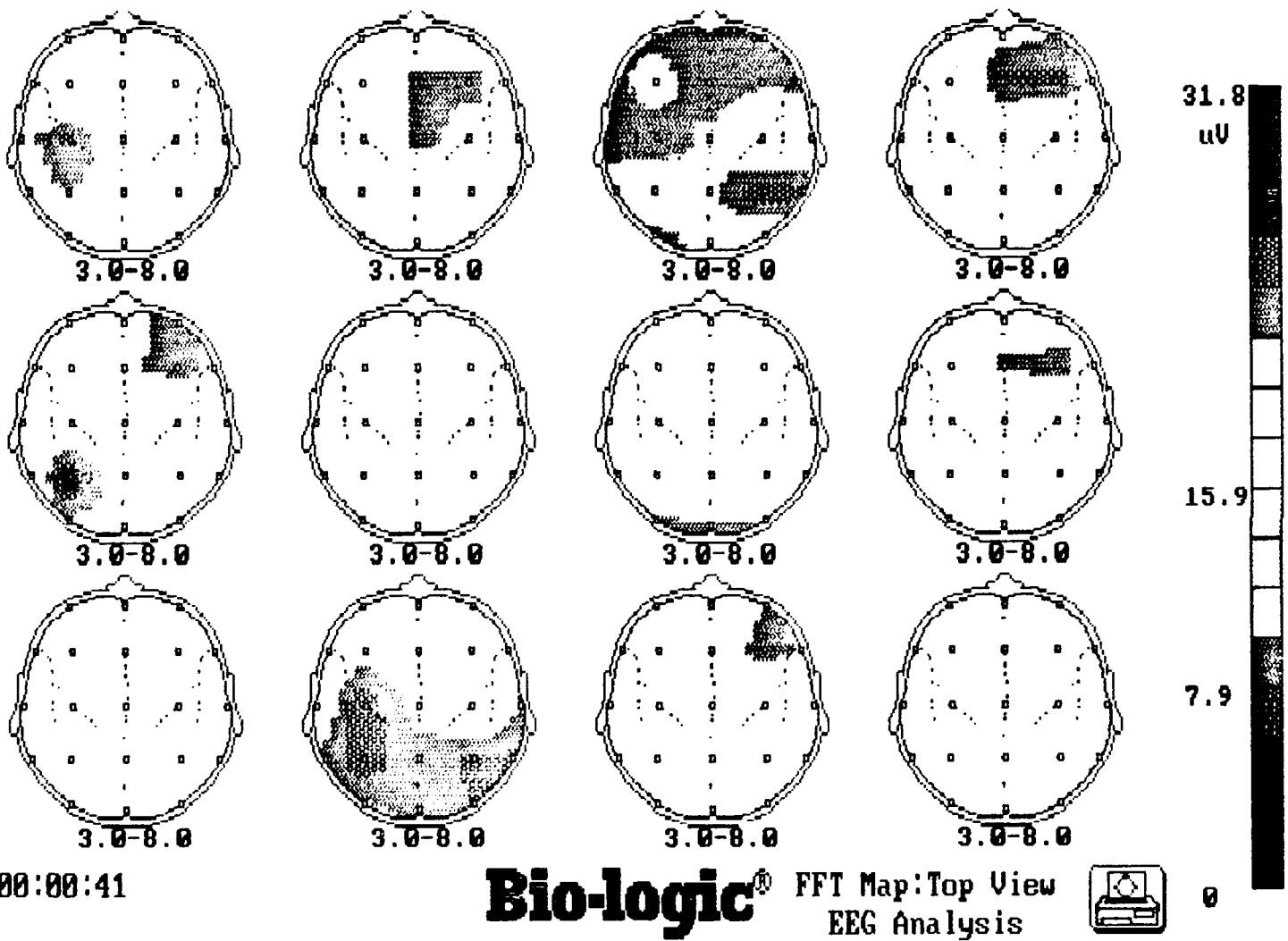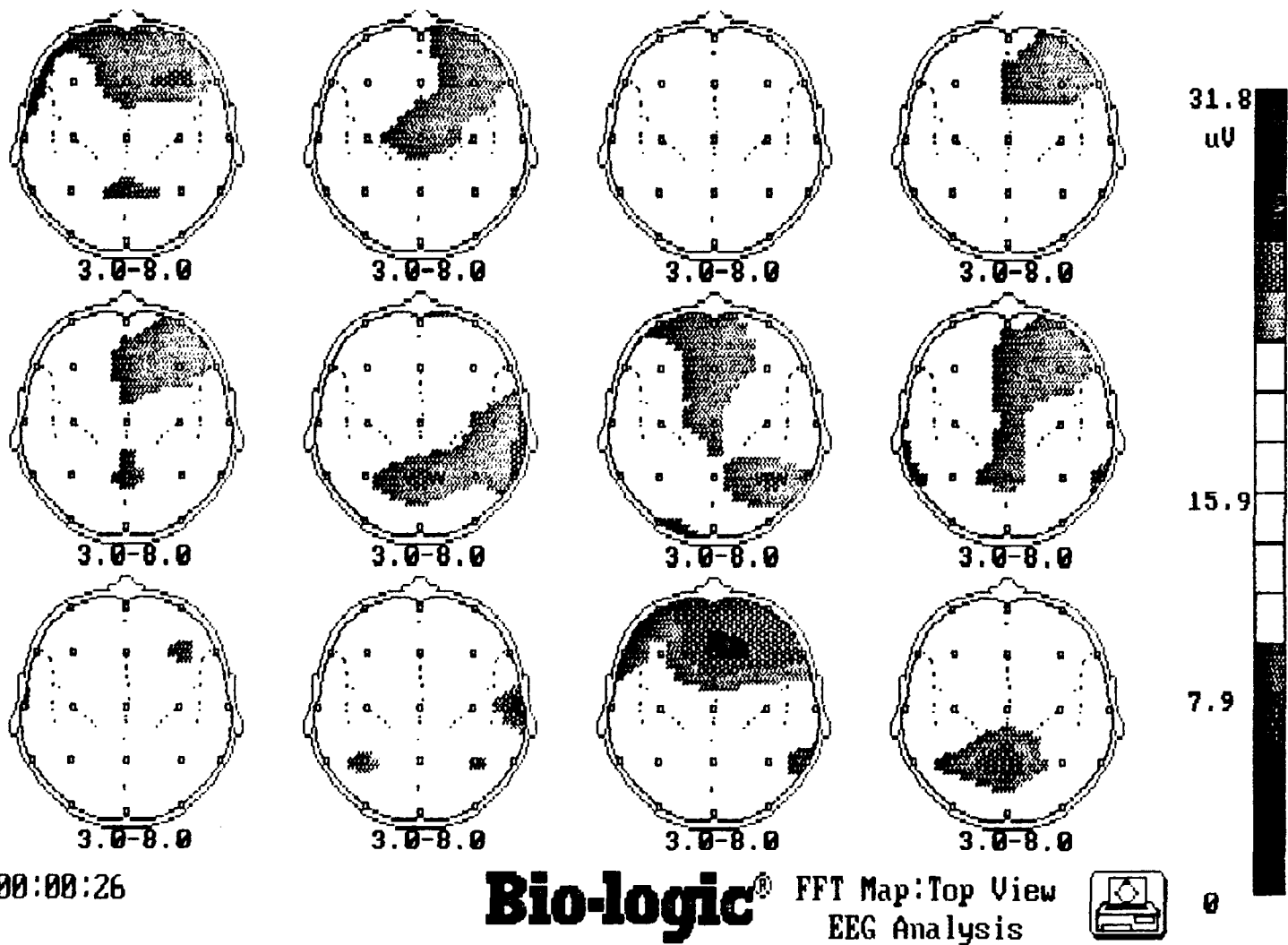
Phenytoin Trial
Subject #5
Frequency 8.0 to 13.0 Hz
Baseline – Sitting at Rest
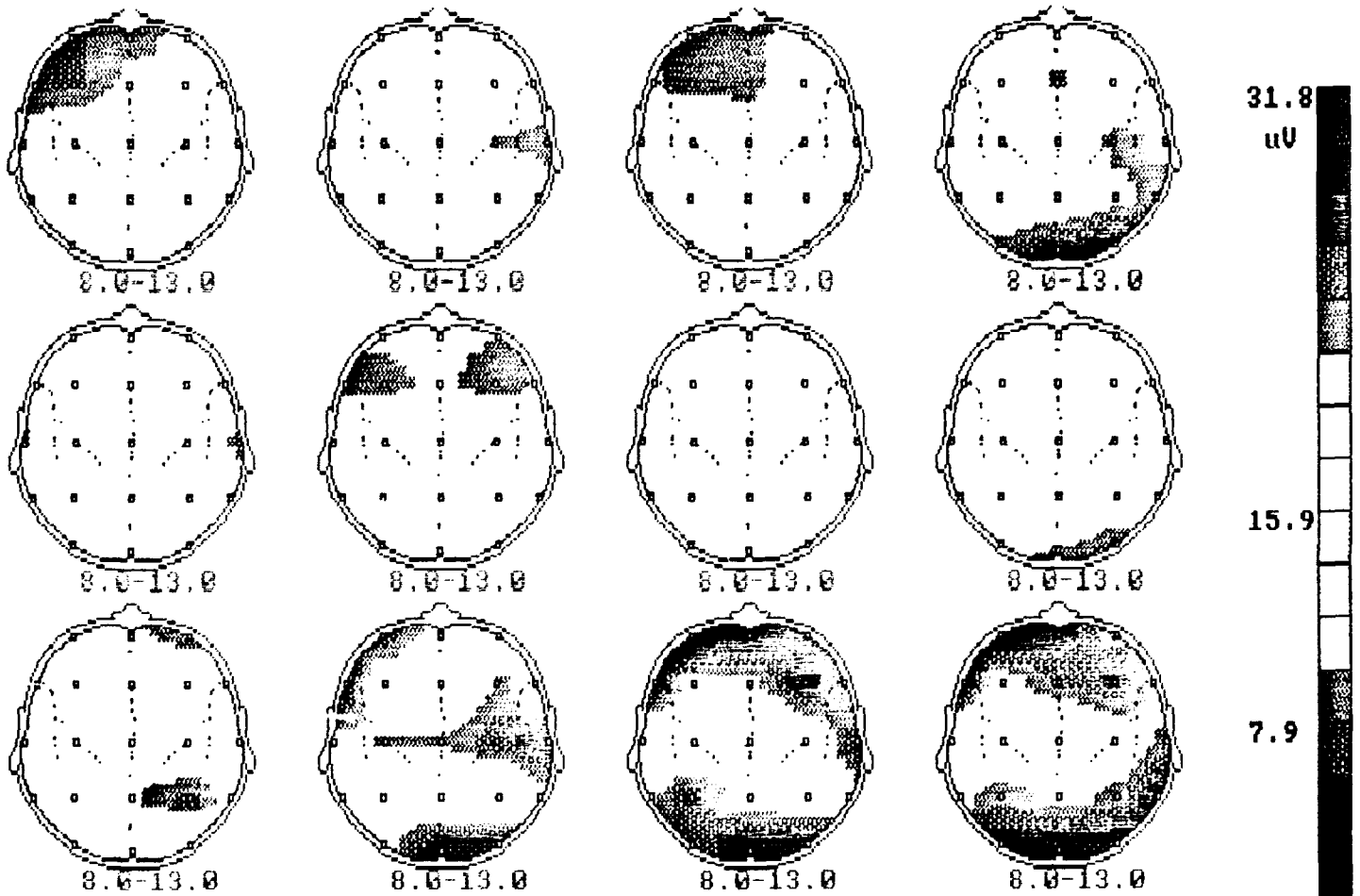
00:00:28
Stop   15:01:48 10/29/90

Bio-logic®   FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Phenytoin Trial
Subject #5
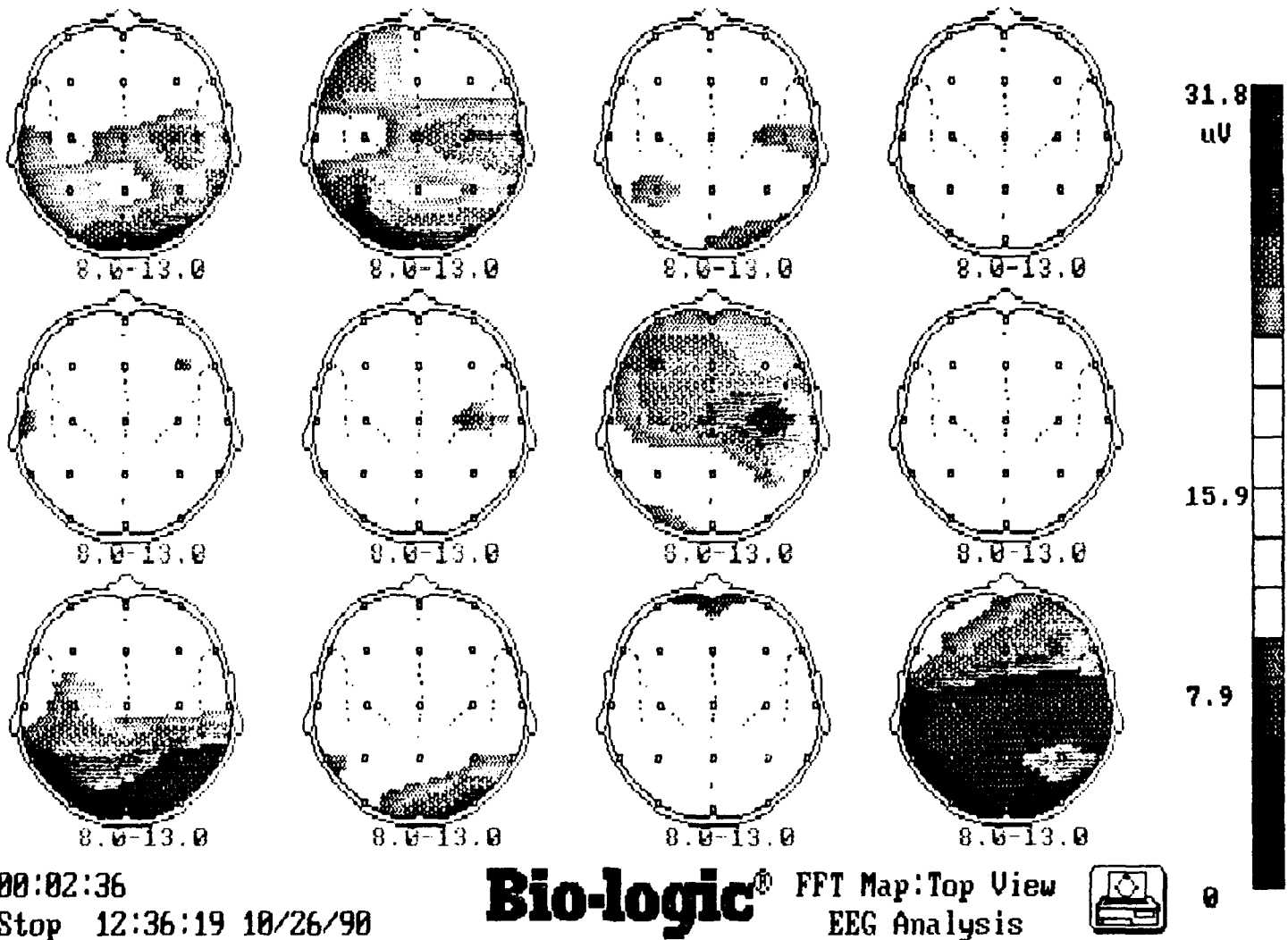Frequency 8.0 to 13.0 Hz
Baseline - Spinning Prior to First HM

00:02:44
Stop 15:01:48 10/29/90

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #5
Frequency 8.0 to 13.0 Hz
Symptom Level 2-3

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

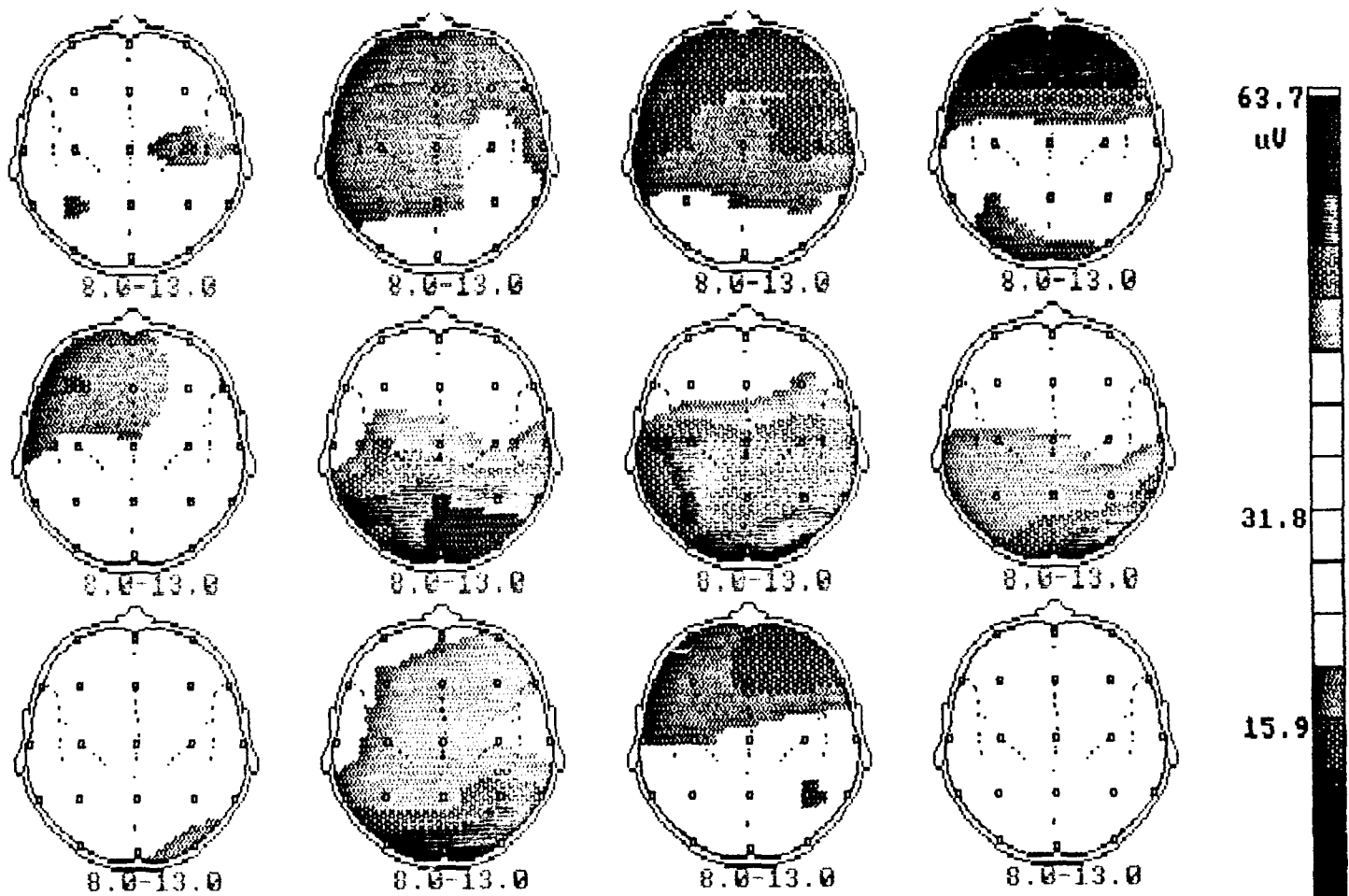8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

31.8
uV

15.9

7.9

0

00:01:11
Stop   15:50:39 10/29/90

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
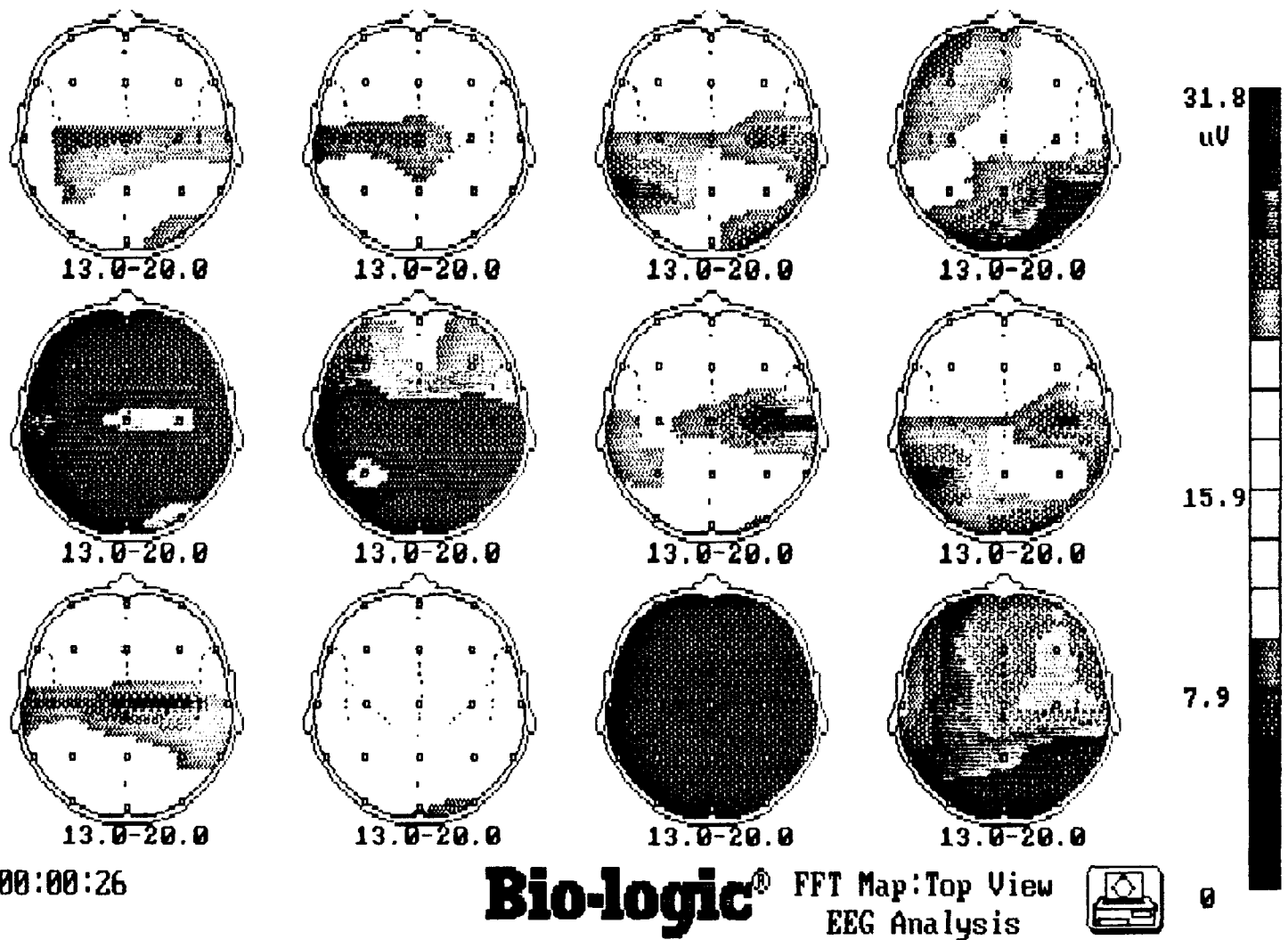Subject #5
Frequency 8.0 to 13.0 Hz
Symptom Level 7

31.8
uV

15.9

7.9

00:00:41
Stop 15:57:51 10/29/90

Bio-logic® FFT Map:Top View
EEG Analysis

0

00:00:26

Bio-logic® FFT Map:Top View
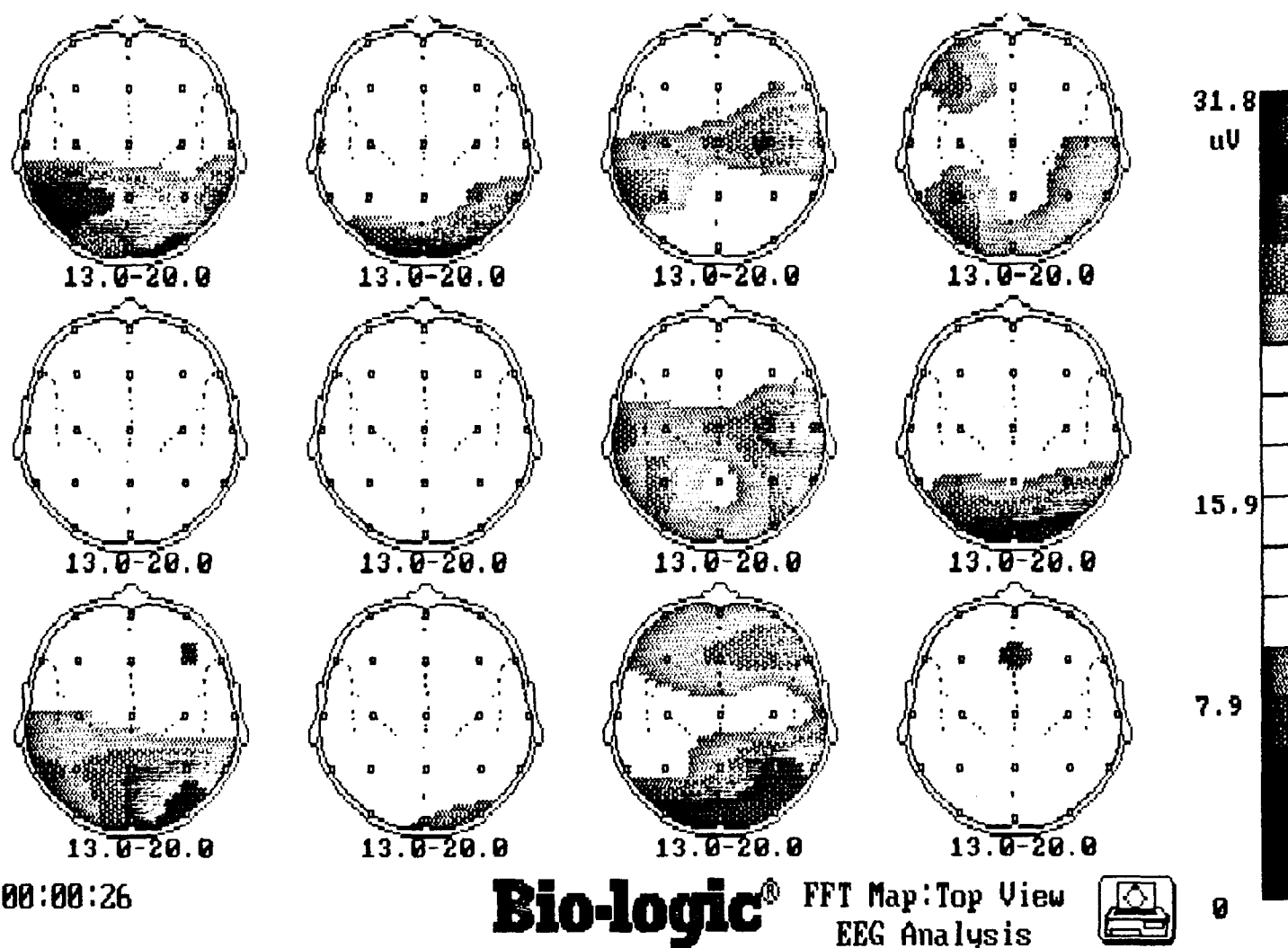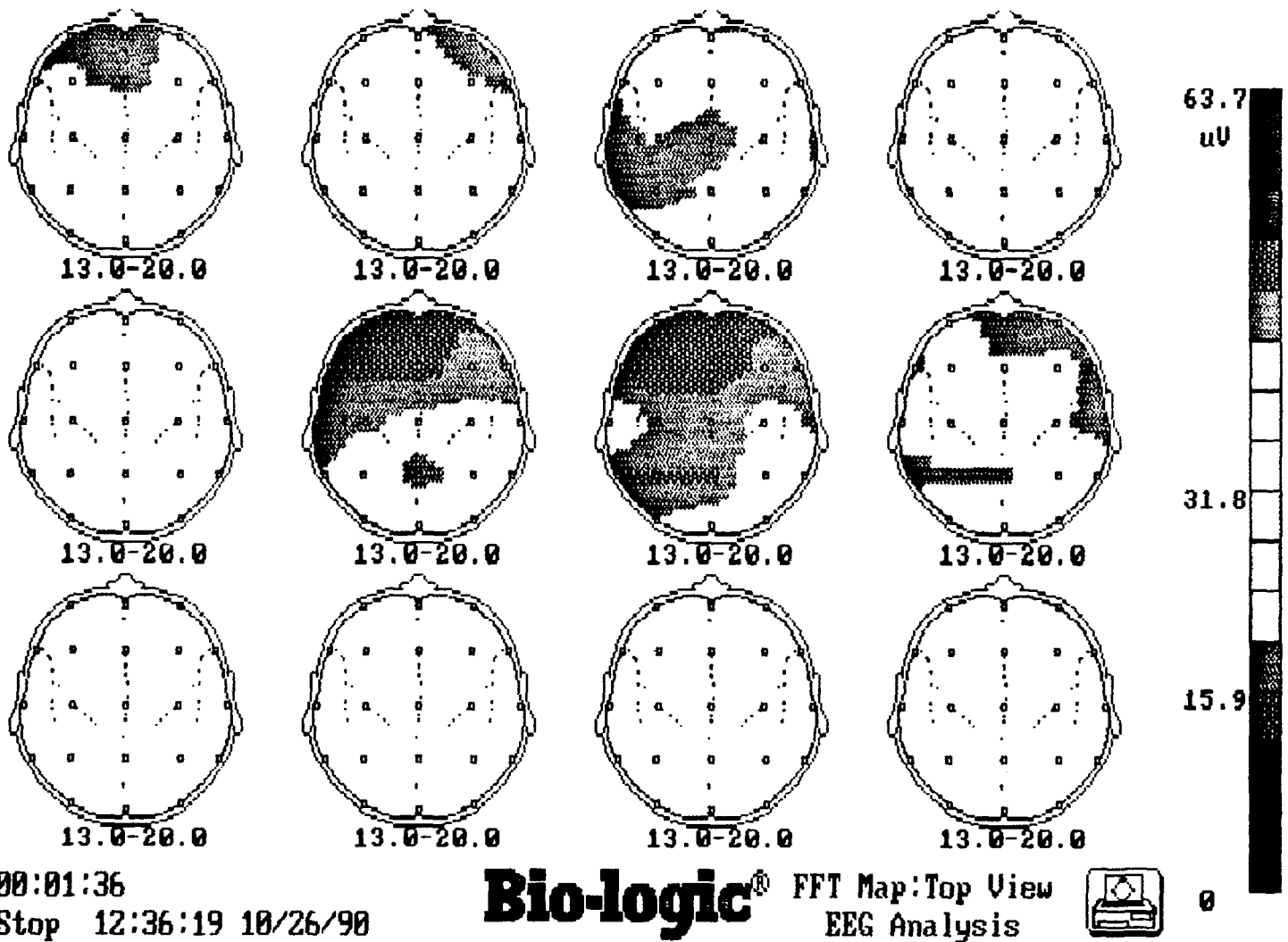EEG Analysis

15.9
uV

7.9

3.9

0

Phenytoin Trial
Subject #5
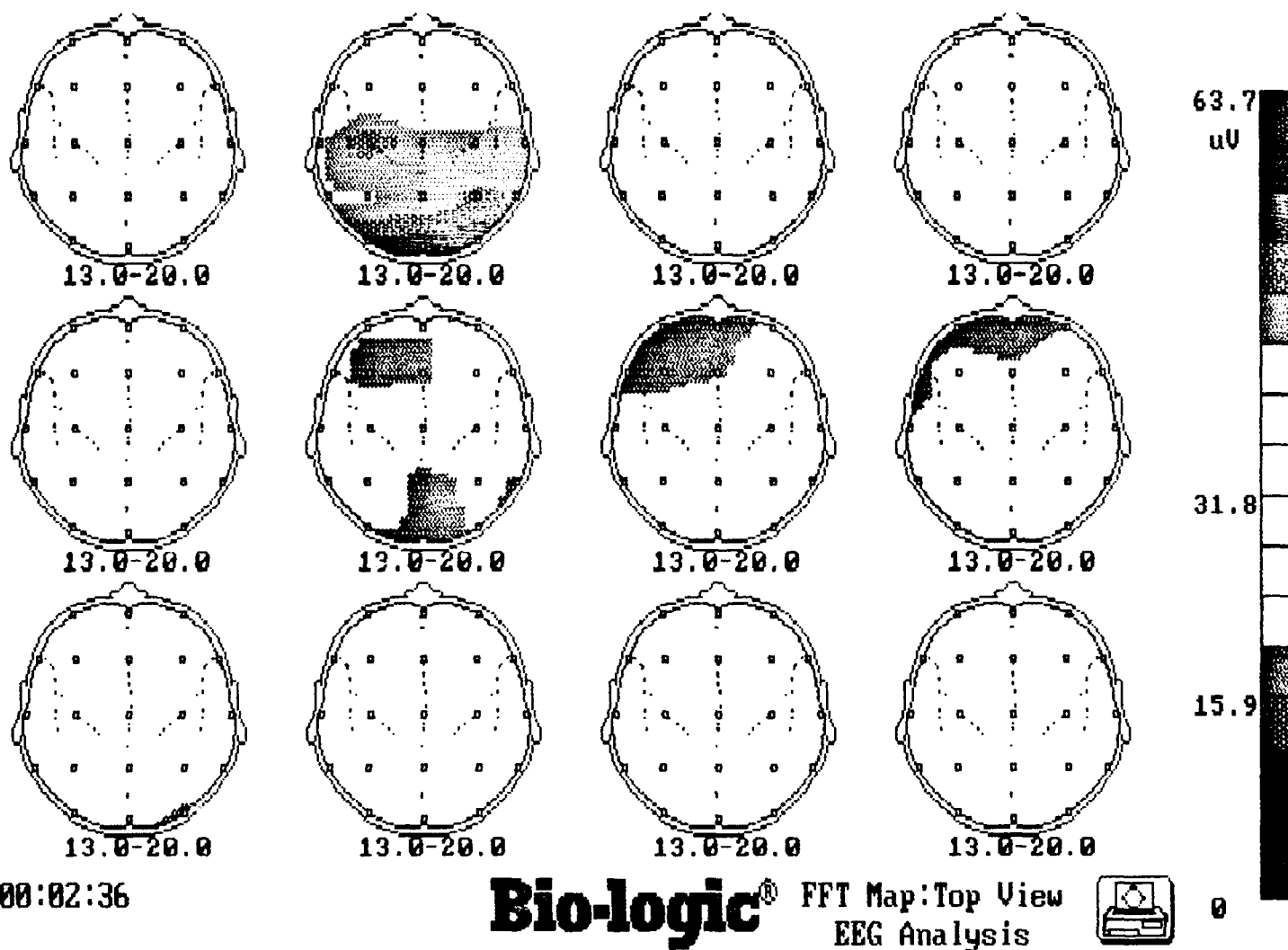Frequency 13.0 to 20.0 Hz
Baseline - Sitting at Rest

Phenytoin Trial
Subject #5
Frequency 13.0 to 20.0 Hz
Baseline - Spinning Prior to First HM

Phenytoin Trial
Subject #5
Frequency 13.0 to 20.0 Hz
Symptom Level 2-3

Phenytoin Trial
Subject #5
Frequency 13.0 to 20.0 Hz
Symptom Level 5

Phenytoin Trial
Subject #5
Frequency 13.0 to 20.0 Hz
Symptom Level 7

31.8
uV

15.9

7.9

00:00:41
Stop   15:57:51 10/29/90

Bio-logic®   FFT Map:Top View
EEG Analysis

0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

Phenytoin Trial
Subject #5
Frequency 13.0 to 20.0 Hz
Symptom Level 9-10

00:00:26   Bio-logic® FFT Map:Top View
            EEG Analysis

183

Phenytoin Trial
Subject #6
Frequency 3.0 to 8.0 Hz
Baseline - Sitting at Rest

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

31.8
uV

15.9

7.9

0

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

184

Phenytoin Trial
Subject #6
Frequency 3.0 to 8.0 Hz
Baseline - Spinning Prior to First HM

3.0-8.0 3.0-8.0 3.0-8.0 3.0-8.0

3.0-8.0 3.0-8.0 3.0-8.0 3.0-8.0

3.0-8.0 3.0-8.0 3.0-8.0 3.0-8.0

31.8
uV

15.9

7.9

0

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #6
Frequency 3.0 to 8.0 Hz
Symptom Level 2-3

31.8 uV

15.9

7.9

0

00:01:36
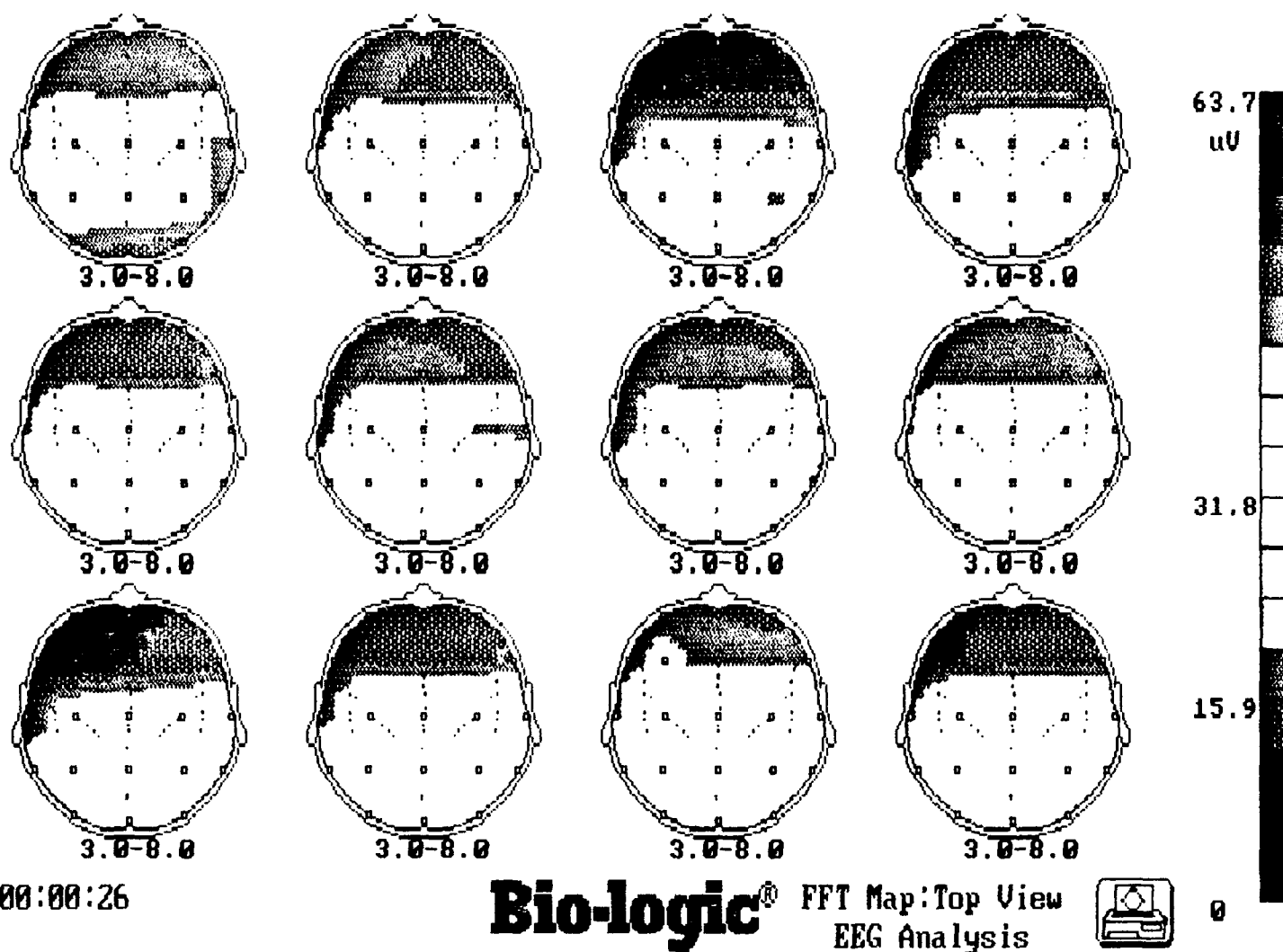Stop 12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #6
Frequency 3.0 to 8.0 Hz
Symptom Level 5

31.8
uV

15.9

7.9

0

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

3.0-8.0   3.0-8.0   3.0-8.0   3.0-8.0

00:02:36
Stop 12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

00:03:04
Stop   12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Phenytoin Trial
Subject #6
Frequency 3.0 to 8.0 Hz
Symptom Level 9-10

00:03:42
Stop   12:36:19 10/26/90

Bio-logic®   FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Baseline - Sitting at Rest

00:00:26   **Bio-logic**® FFT Map:Top View
                          EEG Analysis

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Baseline - Spinning Prior to First HM

00:00:26   Bio-logic® FFT Map:Top View
            EEG Analysis
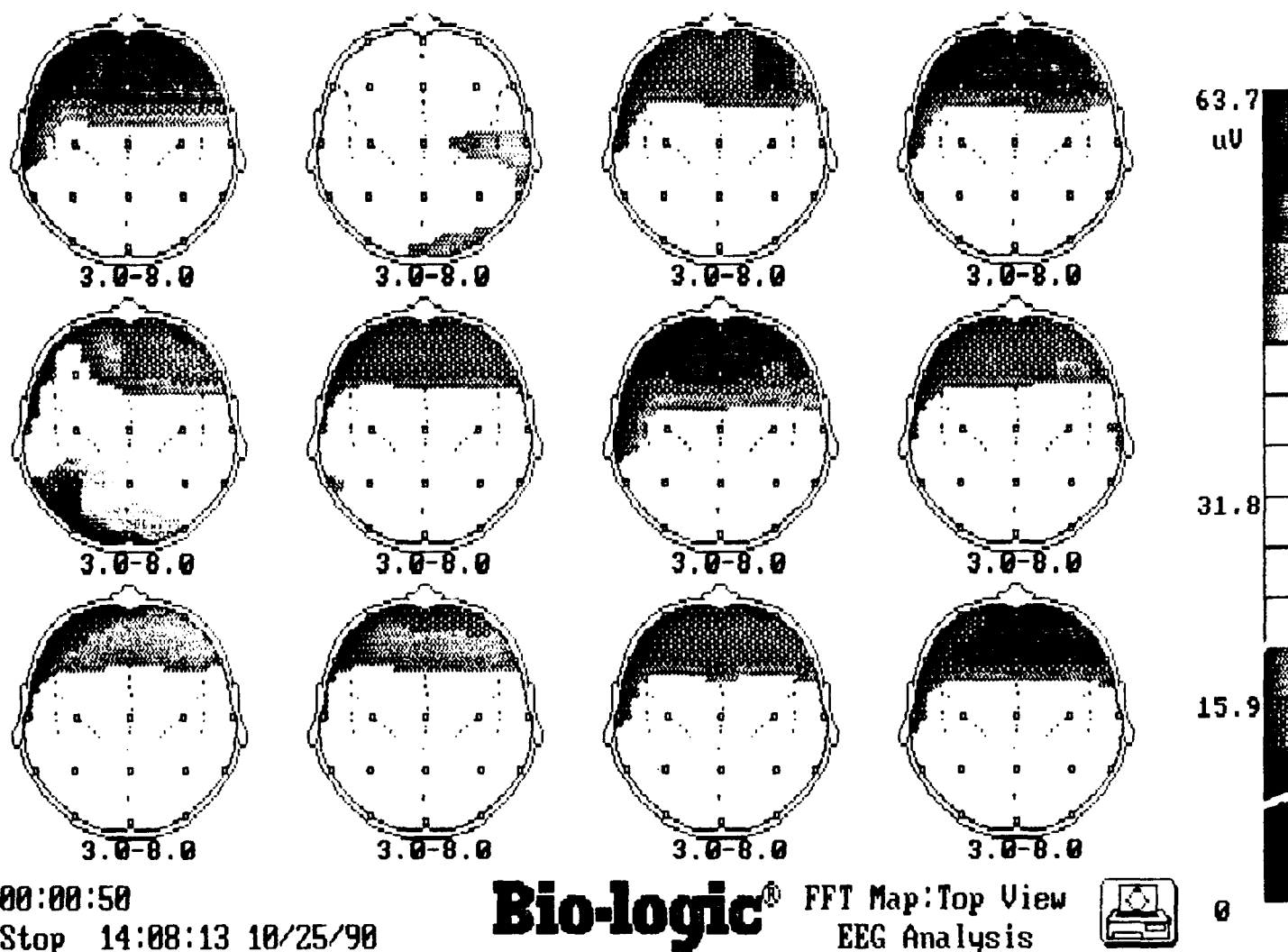
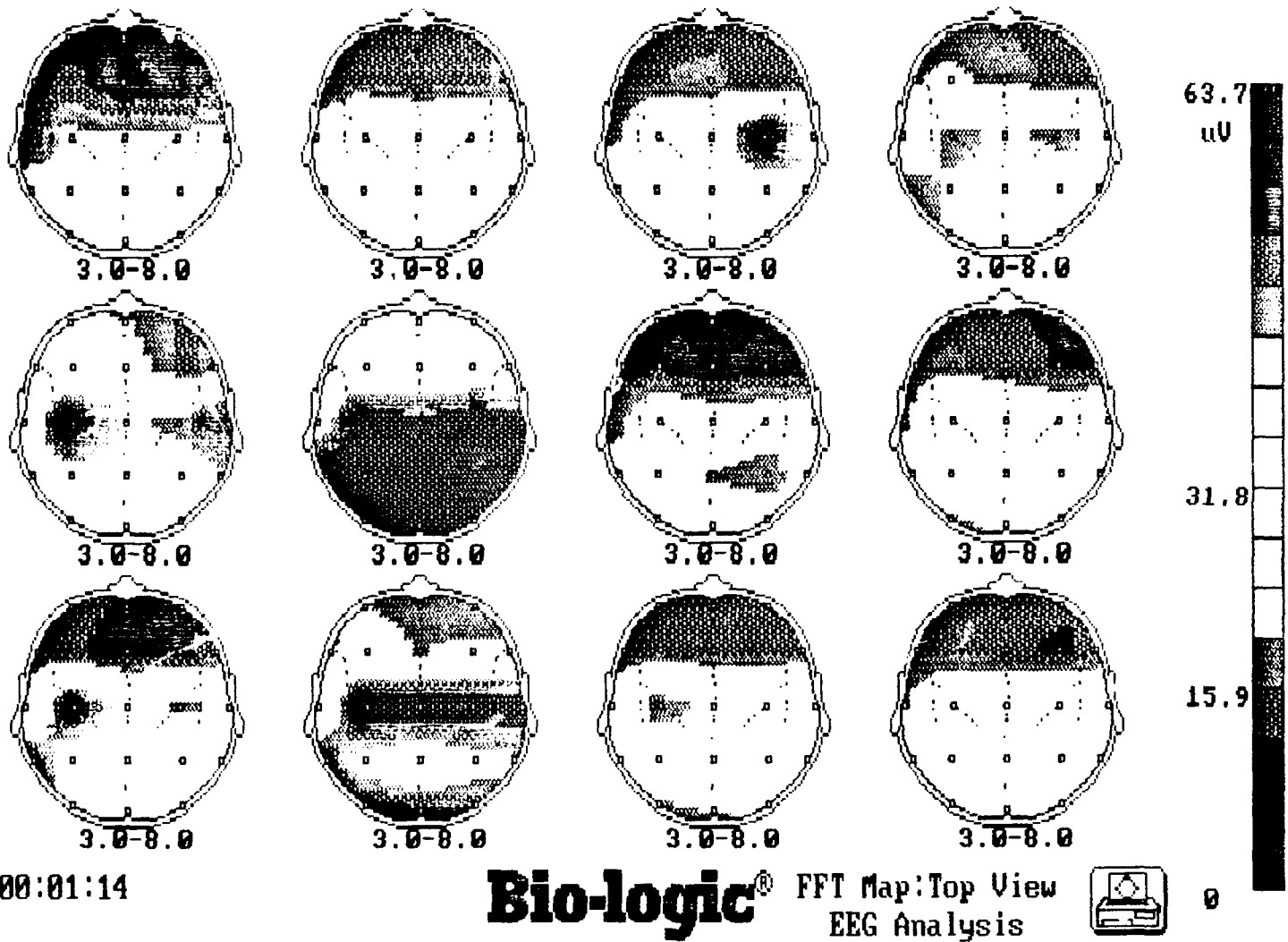191

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Symptom Level 2-3

00:01:36
Stop 12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Symptom Level 5

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

31.8 uV

15.9

7.9

0

00:02:36
Stop   12:36:19 10/26/90

Bio-logic®   FFT Map:Top View
EEG Analysis

193

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Symptom Level 7

00:03:04
Stop   12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

194

Phenytoin Trial
Subject #6
Frequency 8.0 to 13.0 Hz
Symptom Level 9-10

00:03:42

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #6
Frequency 13.0 to 20.0 Hz
Baseline - Sitting at Rest

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

31.8 uV

15.9

7.9

0

Phenytoin Trial
Subject #6
Frequency 13.0 to 20.0 Hz
Baseline – Spinning Prior to First HM

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

31.8 uV

15.9

7.9

0

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #6
Frequency 13.0 to 20.0 Hz
Symptom Level 2-3

00:01:36
Stop 12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

Phenytoin Trial
Subject #6
Frequency 13.0 to 20.0 Hz
Symptom Level 5

63.7
uV

31.8

15.9

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

00:02:36   **Bio·logic**® FFT Map:Top View
EEG Analysis

0

199

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

63.7
uV

31.8

15.9

0

00:03:04
Stop 12:36:19 10/26/90

Bio-logic® FFT Map:Top View
EEG Analysis

200

Phenytoin Trial
Subject #6
Frequency 13.0 to 20.0 Hz
Symptom Level 9-10

00:00:26

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 3.0 to 8.0 Hz
Baseline - Spinning Prior to First HM

00:01:00

Bio-logic® FFT Map:Top View
EEG Analysis

63.7
uV

31.8

15.9

0

Placebo Trial
Subject #1
Frequency 3.0 to 8.0 Hz
Symptom Level 2-3

63.7
uV

31.8

15.9

00:00:26　Bio-logic® FFT Map:Top View
EEG Analysis

0

204

Placebo Trial
Subject #1
Frequency 3.0 to 8.0 Hz
Symptom Level 5

00:00:50
Stop   14:08:13 10/25/90

Bio-logic®   FFT Map:Top View
EEG Analysis

63.7
uV

31.8

15.9

0

Placebo Trial
Subject #1
Frequency 3.0 to 8.0 Hz
Symptom Level 7

00:01:14

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 3.0 to 8.0 Hz
Symptom Level 9-10

63.7
uV

31.8

15.9

00:01:38
Stop   14:08:13 10/25/90

Bio-logic® FFT Map:Top View
EEG Analysis

0

Placebo Trial
Subject #1
Frequency 8.0 to 13.0 Hz
Baseline - Sitting at Rest

Placebo Trial
Subject #1
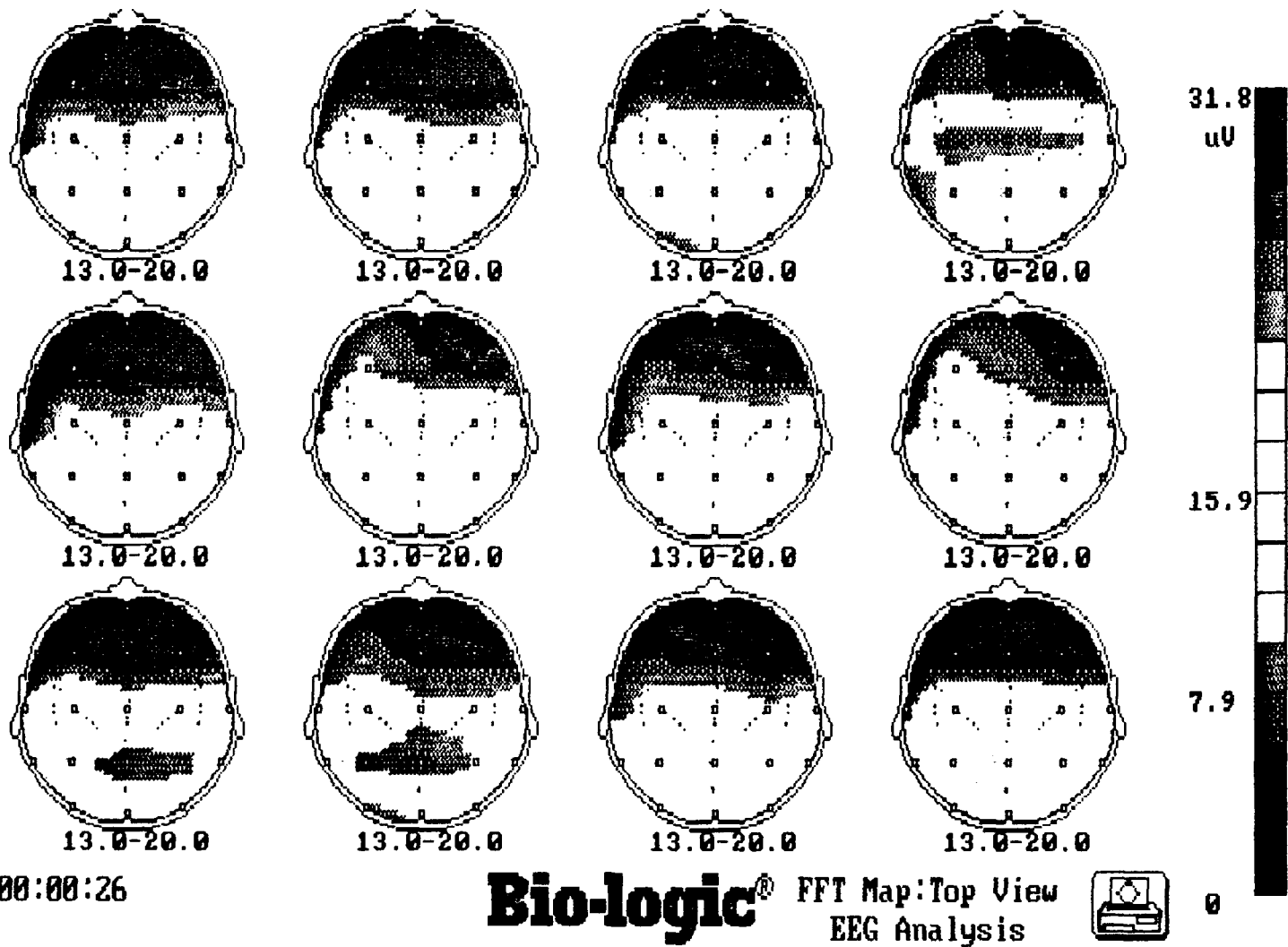## Frequency 8.0 to 13.0 Hz
Baseline - Spinning Prior to First HM

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

8.0-13.0   8.0-13.0   8.0-13.0   8.0-13.0

63.7 uV

31.8

15.9

0

00:01:00

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 8.0 to 13.0 Hz
Symptom Level 2-3

00:00:26   **Bio-logic**® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 8.0 to 13.0 Hz
Symptom Level 5

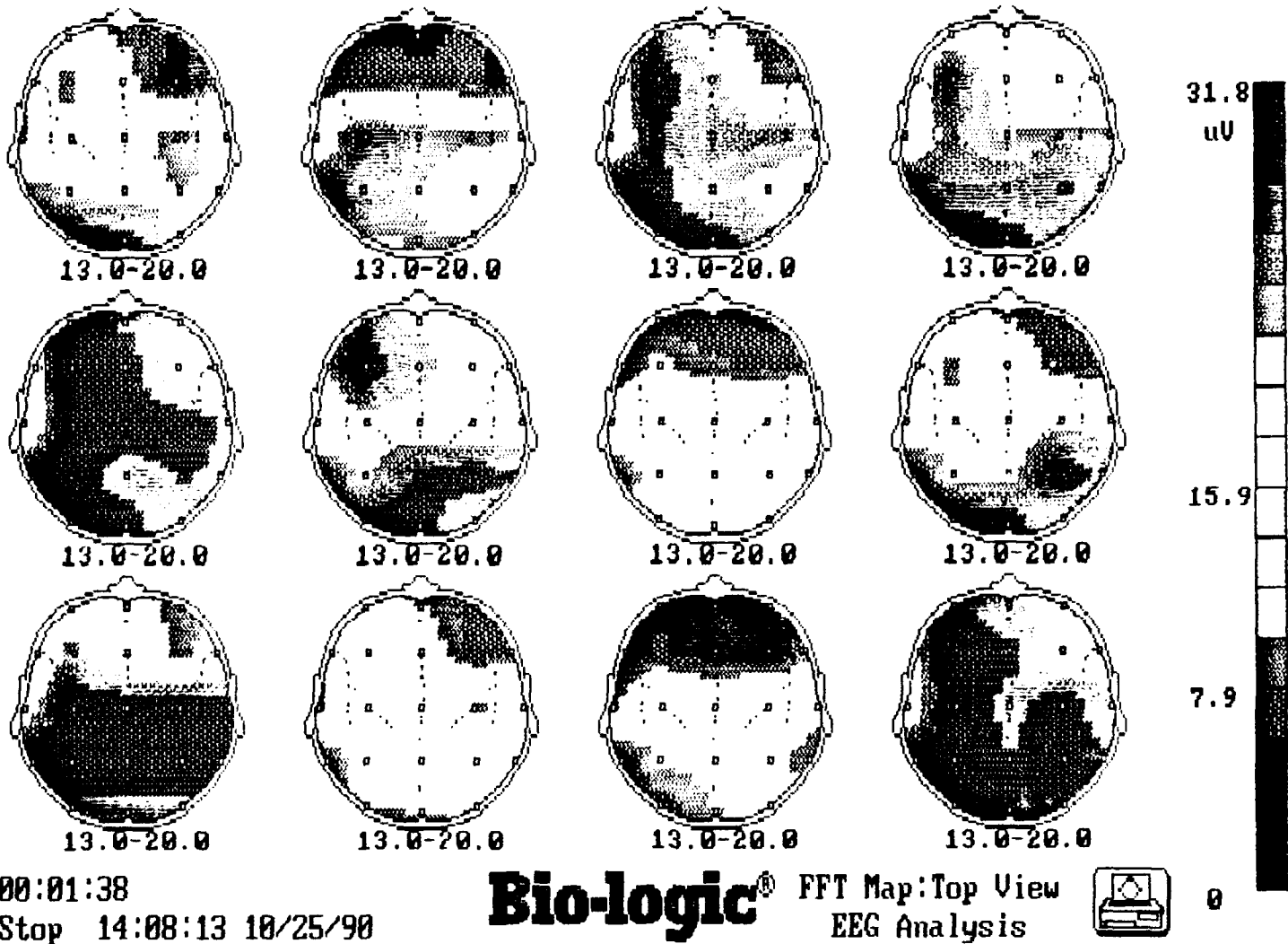00:00:50
Stop   14:08:13 10/25/90

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
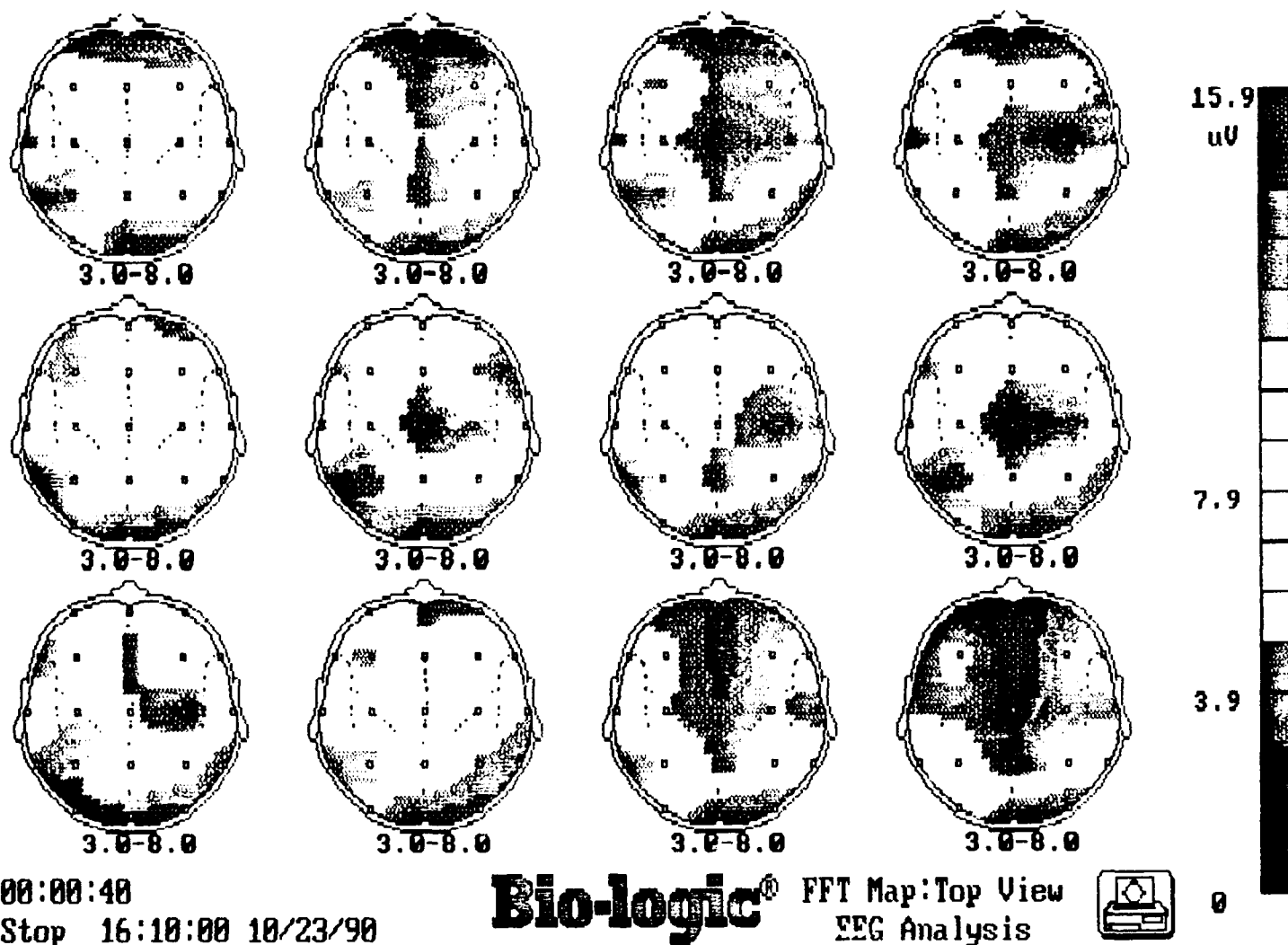Frequency 8.0 to 13.0 Hz
Symptom Level 7

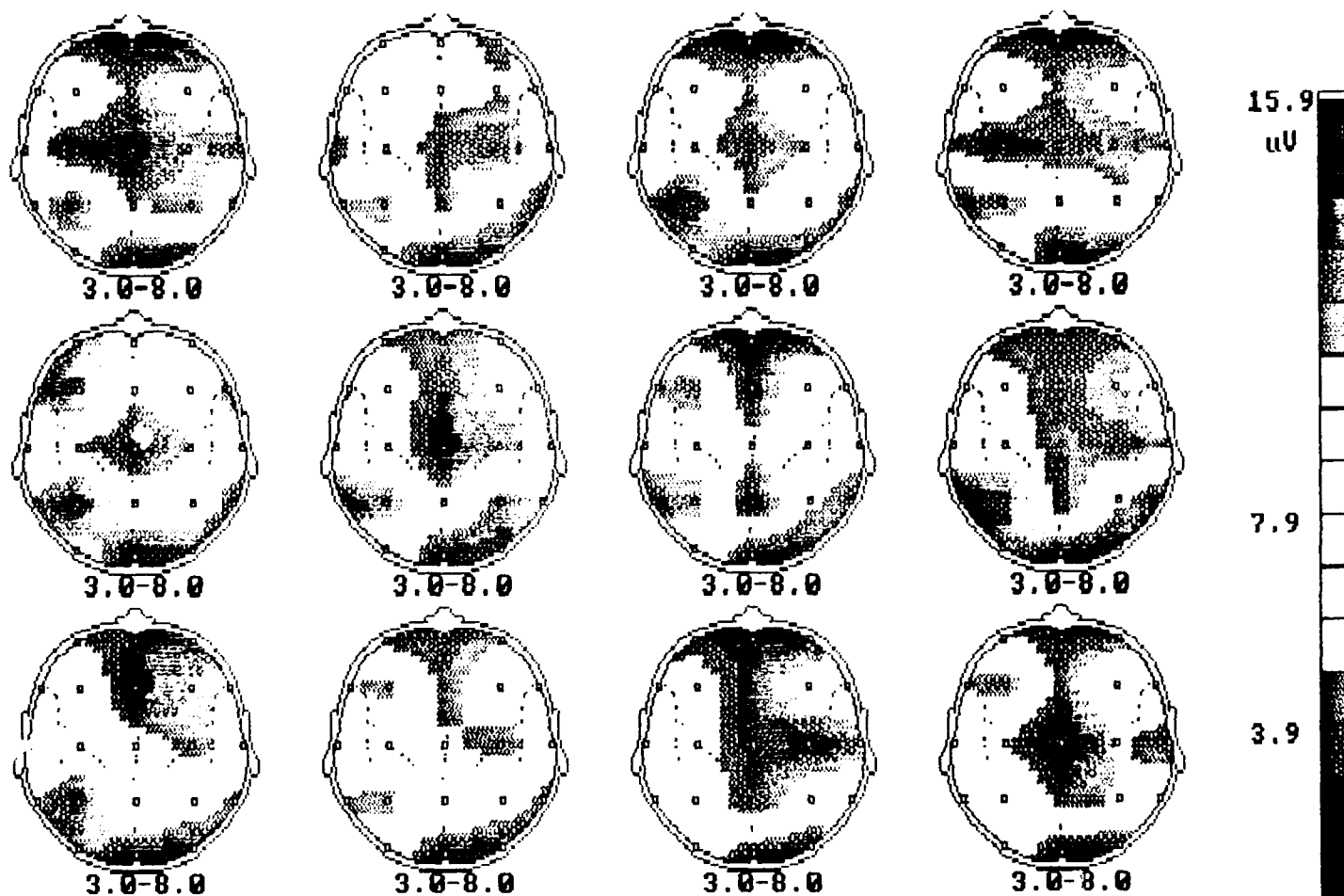00:01:14

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 8.0 to 13.0 Hz
Symptom Level 9-10

Placebo Trial
Subject #1
Frequency 13.0 to 20.0 Hz
Baseline - Sitting at Rest
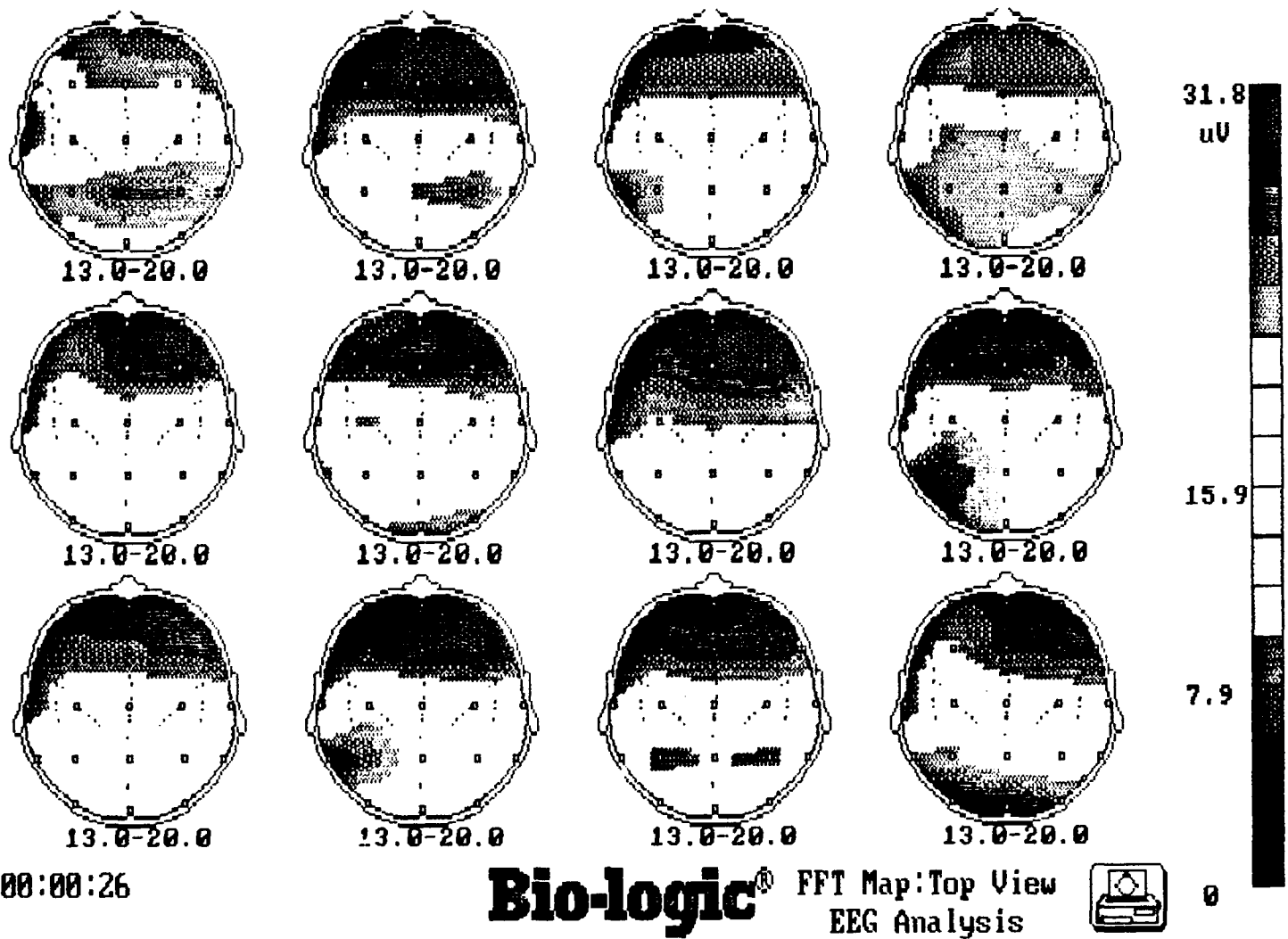
Placebo Trial
Subject #1
Frequency 13.0 to 20.0 Hz
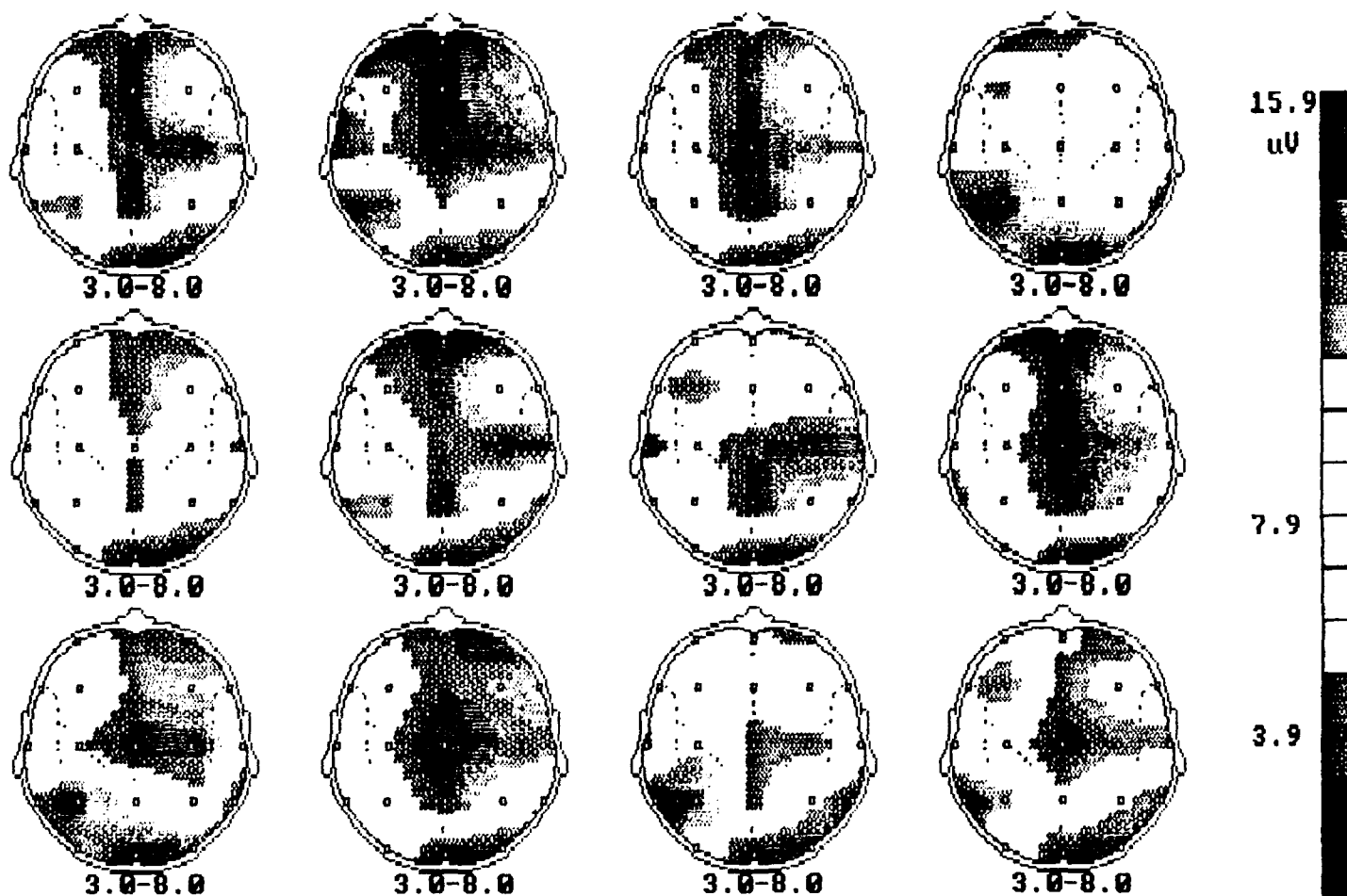**Baseline - Spinning Prior to First HM**

00:01:00

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
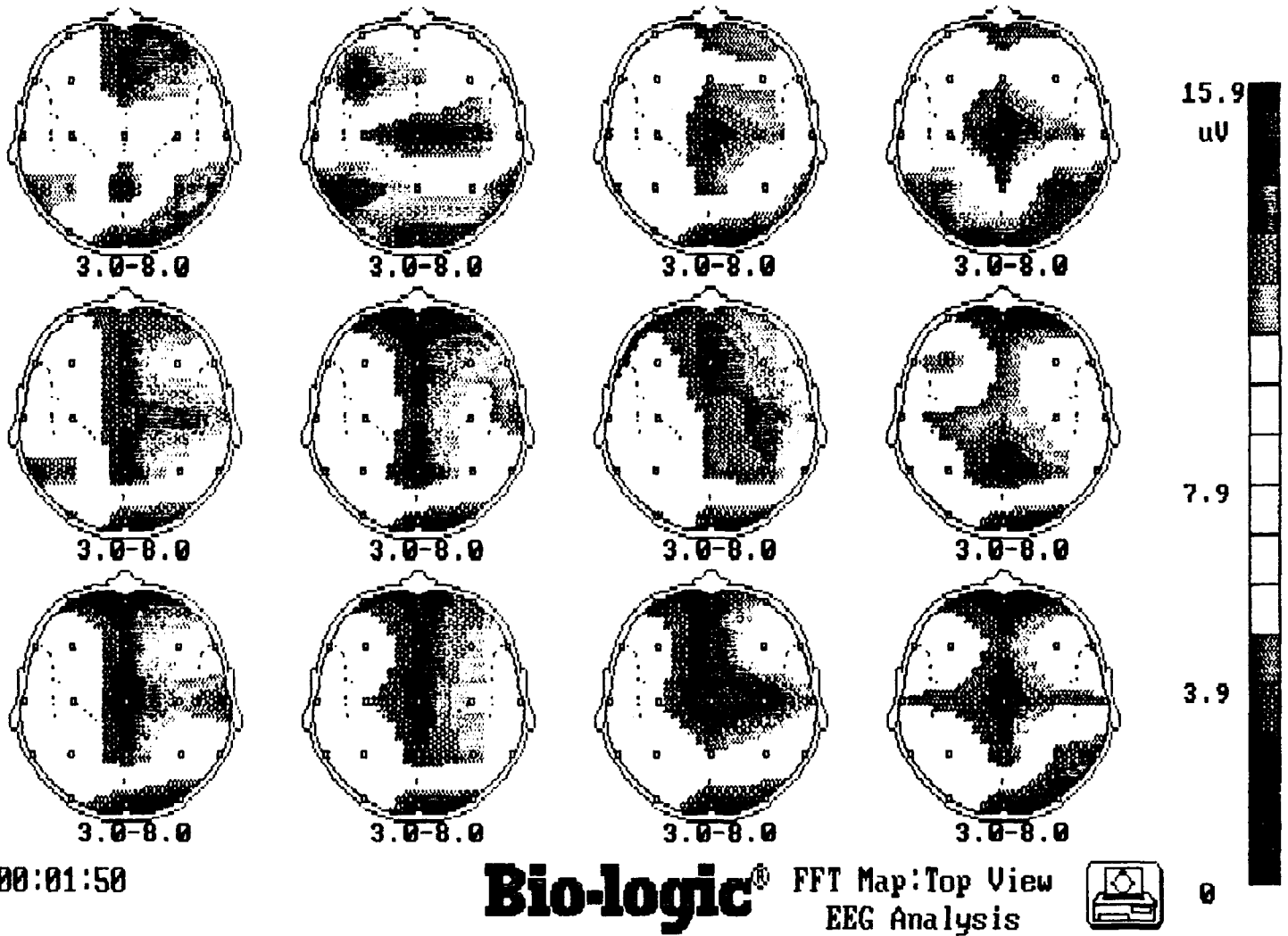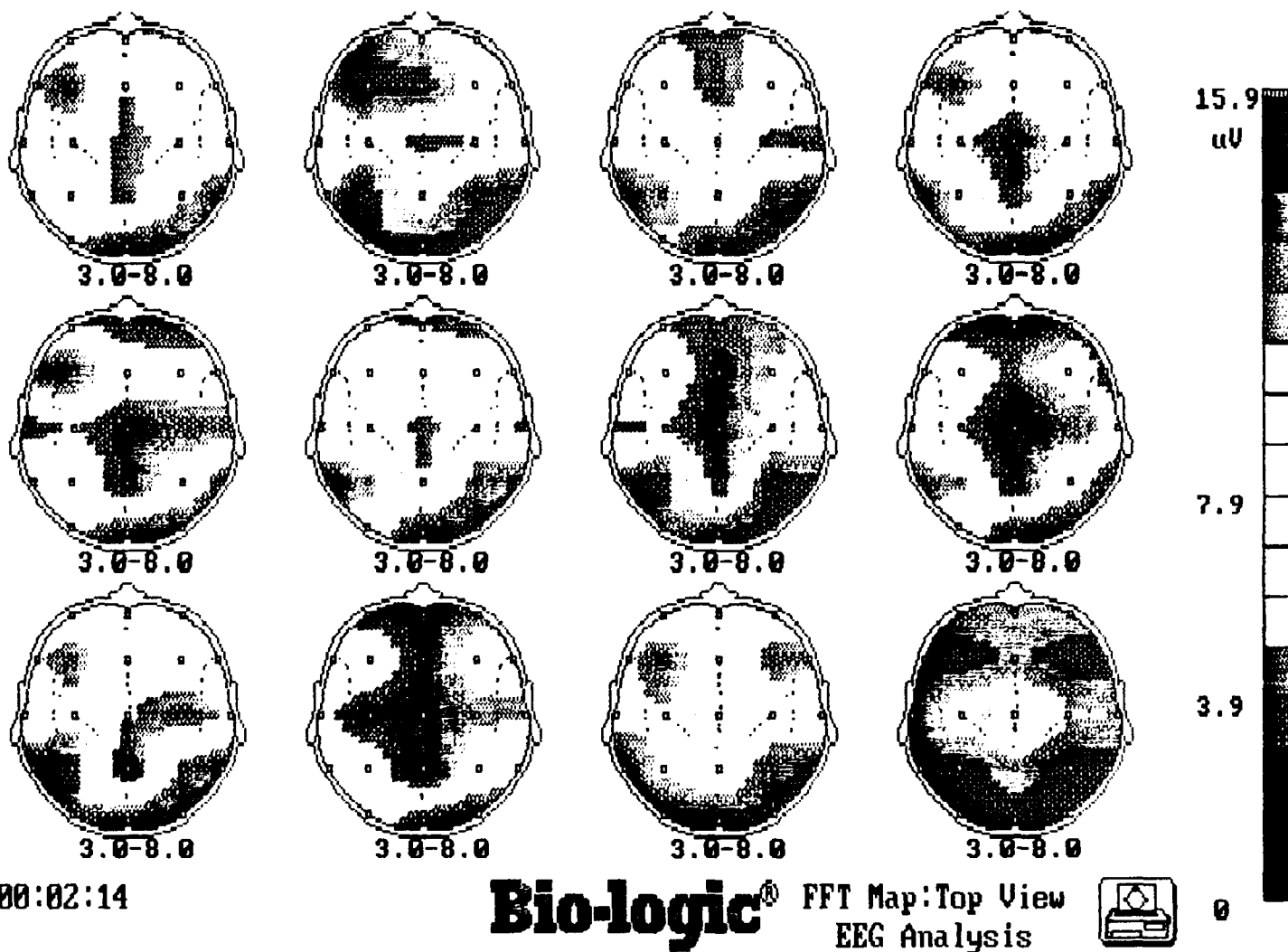Frequency 13.0 to 20.0 Hz
Symptom Level 2-3

Placebo Trial
Subject #1
Frequency 13.0 to 20.0 Hz
Symptom Level 5

00:00:50
Stop   14:08:13 10/25/90

Bio-logic®   FFT Map:Top View
EEG Analysis

31.8
uV

15.9

7.9

0

Placebo Trial
Subject #1
Frequency 13.0 to 20.0 Hz
Symptom Level 7

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

31.8
uV

15.9

7.9

0
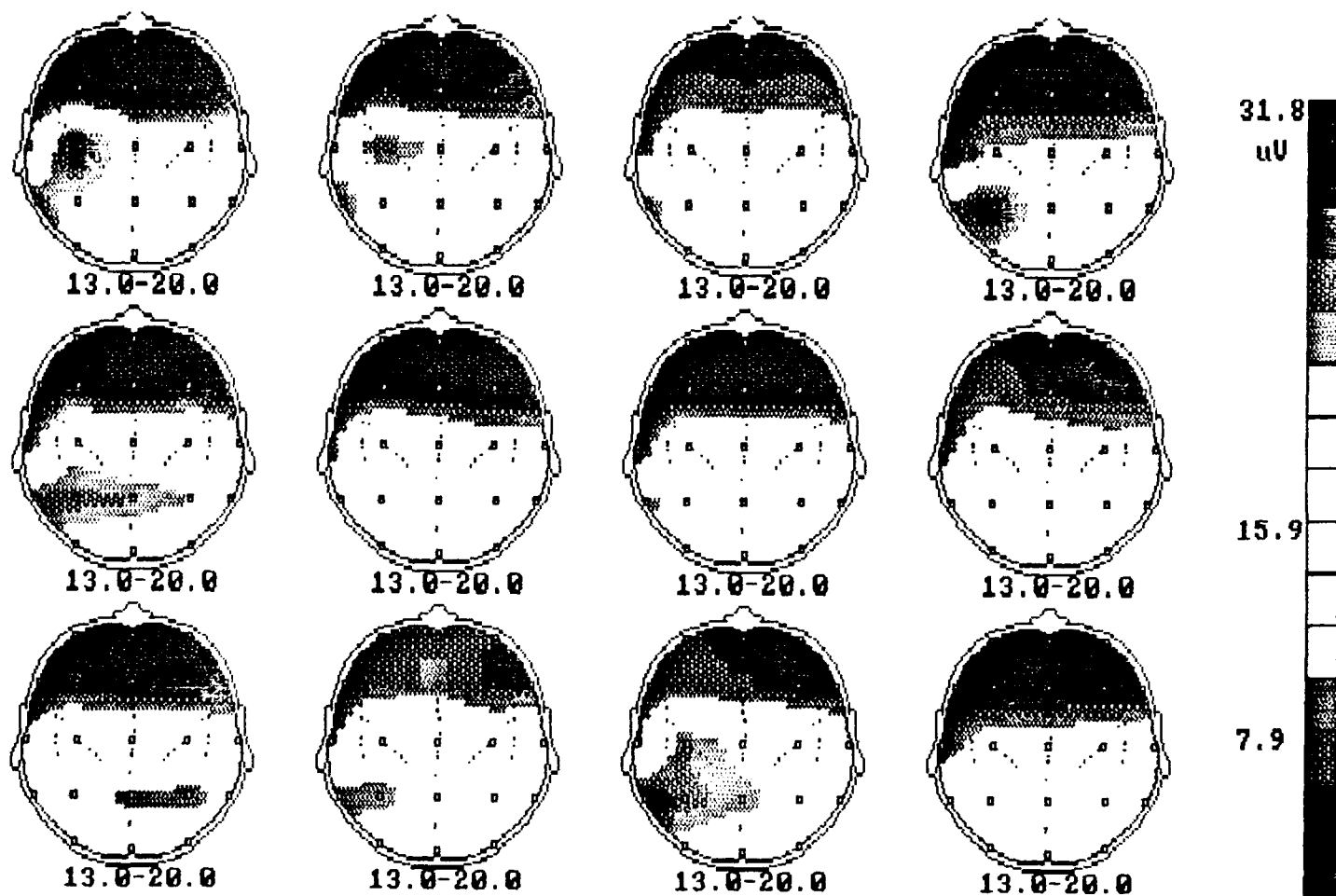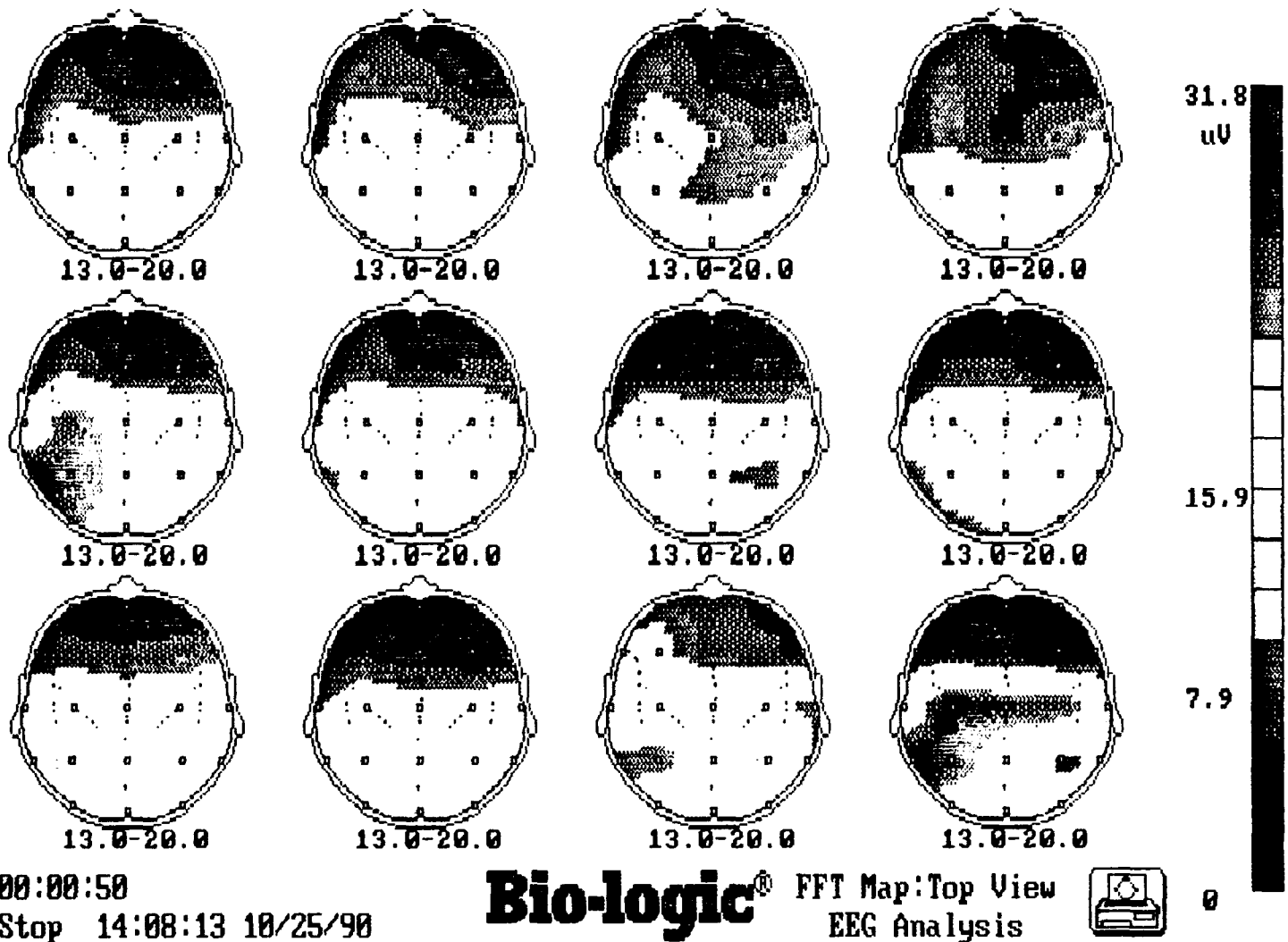
00:01:14
Stop 14:08:13 10/25/90

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #1
Frequency 13.0 to 20.0 Hz
Symptom Level 9-10

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

13.0-20.0

31.8
uV

15.9

7.9

0

00:01:38
Stop 14:08:13 10/25/90

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
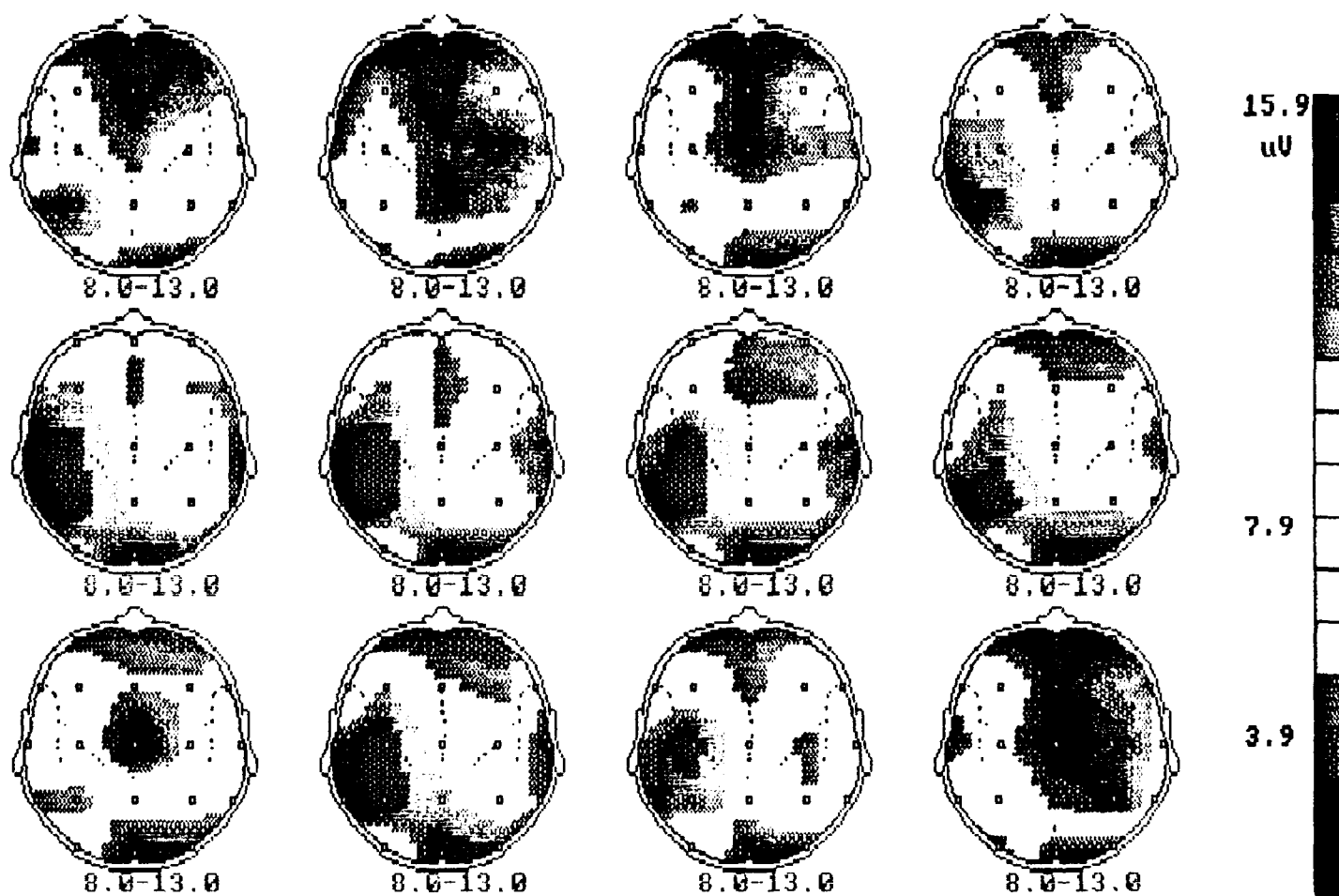Baseline - Sitting at Rest

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
Baseline - Spinning Prior to First HM

00:00:50

Bio-logic® FFT Map:Top View
EEG Analysis

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
Symptom Level 2-3

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
Symptom Level 5

00:01:50

Bio-logic® FFT Map:Top View
EEG Analysis

15.9
uV

7.9

3.9

0

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
Symptom Level 7

00:02:14

Bio-logic® FFT Map:Top View
EEG Analysis

15.9
uV

7.9

3.9

0

Placebo Trial
Subject #8
Frequency 3.0 to 8.0 Hz
Symptom Level 9-10

00:02:38
Stop 13:45:32 10/24/90

Bio-logic® FFT Map:Top View
                EEG Analysis

15.9
uV

7.9

3.9

0
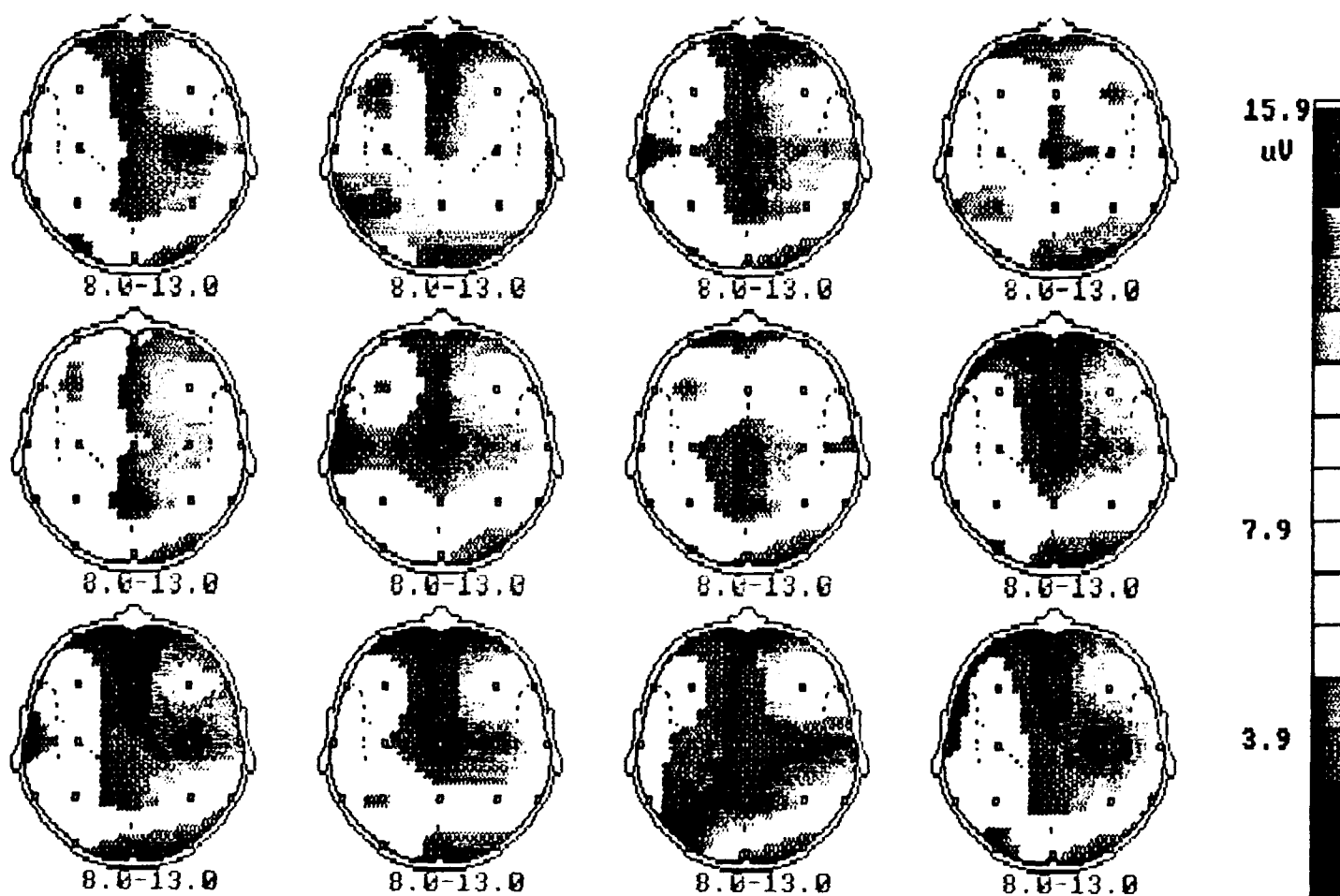
Placebo Trial
Subject #8
Frequency 8.0 to 13.0 Hz
Baseline - Sitting at Rest

Placebo Trial
Subject #8
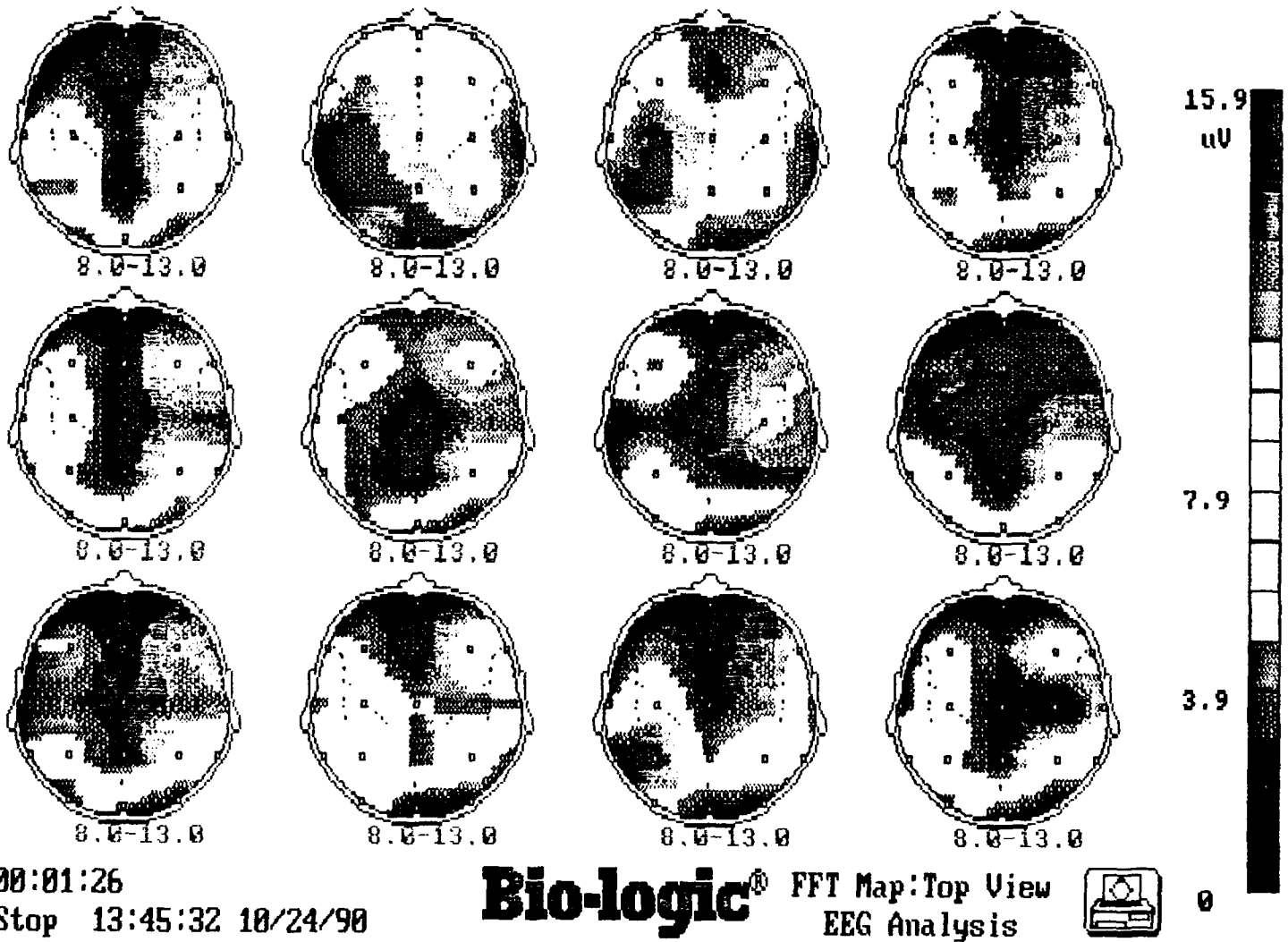Frequency 8.0 to 13.0 Hz
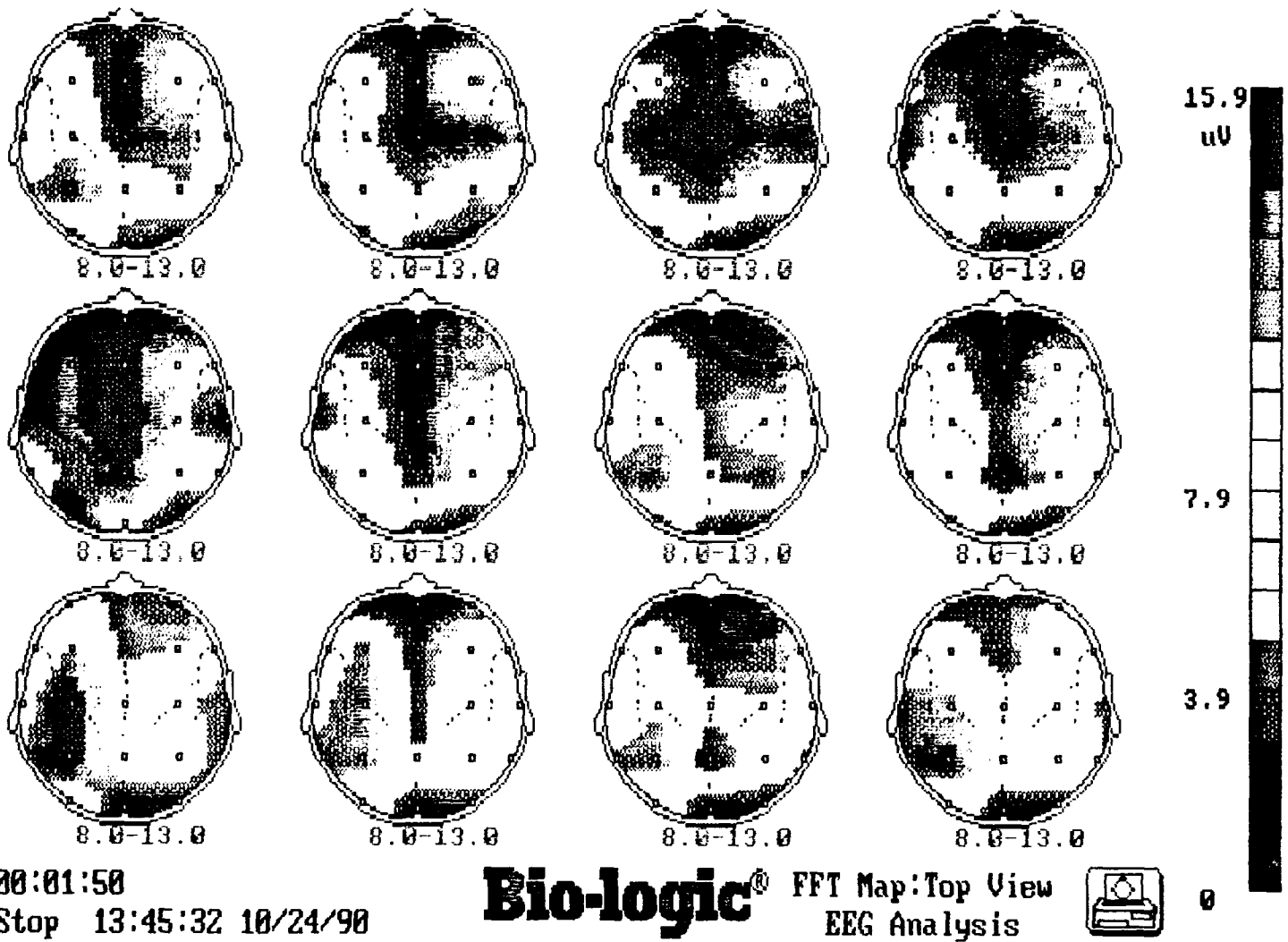Baseline - Spinning Prior to First HM

00:00:50
Stop 13:45:32 10/24/90
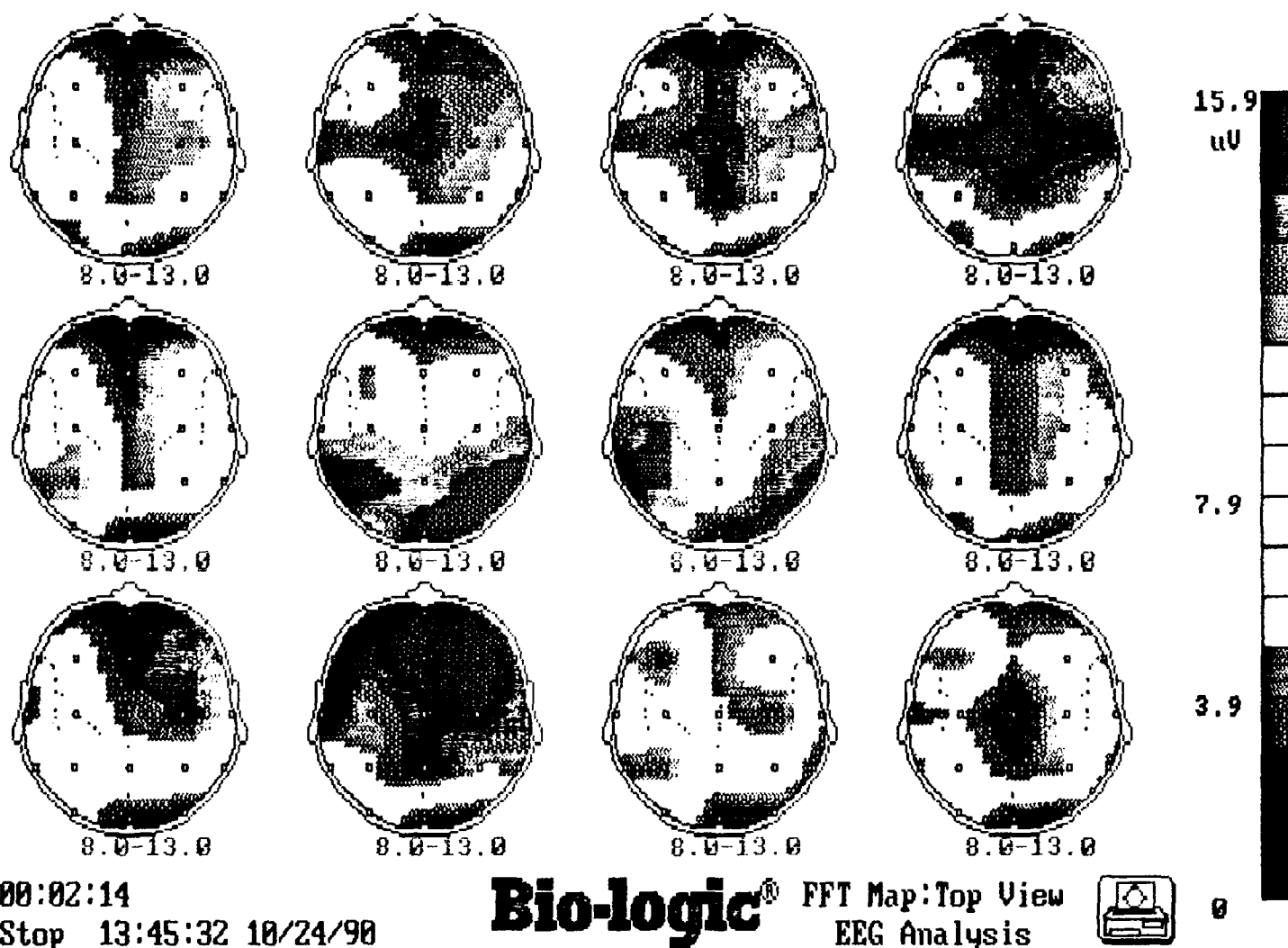
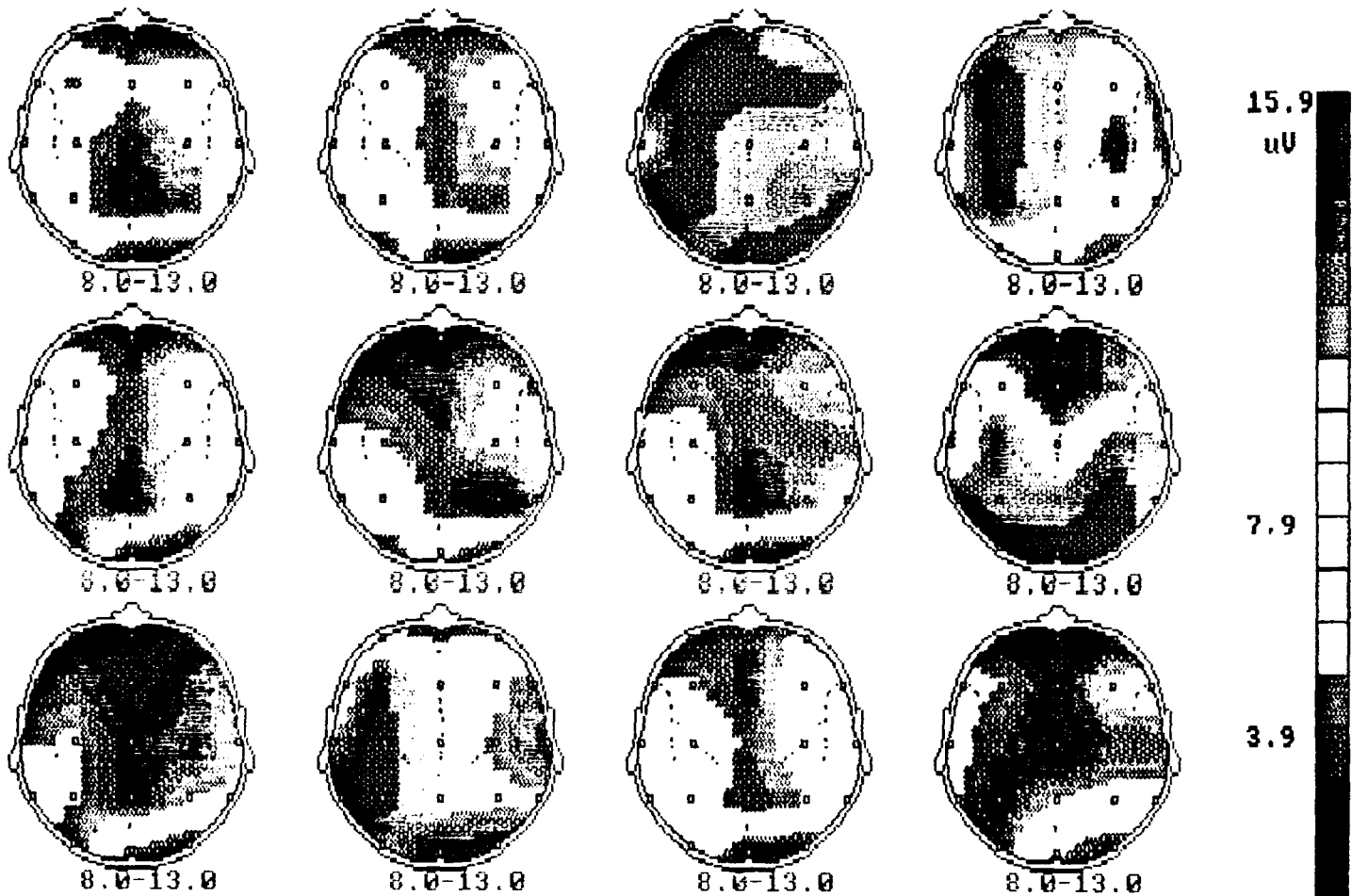Bio-logic® FFT Map:Top View
EEG Analysis

15.9 uV

7.9

3.9

0

Placebo Trial
Subject #8
Frequency 8.0 to 13.0 Hz
Symptom Level 2-3

Placebo Trial
Subject #8
Frequency 8.0 to 13.0 Hz
Symptom Level 5

Placebo Trial
Subject #8
Frequency 8.0 to 13.0 Hz
Symptom Level 7

15.9
uV

7.9

3.9

00:02:14
Stop 13:45:32 10/24/90

Bio-logic® FFT Map:Top View
EEG Analysis

0

Placebo Trial
Subject #8
Frequency 8.0 to 13.0 Hz
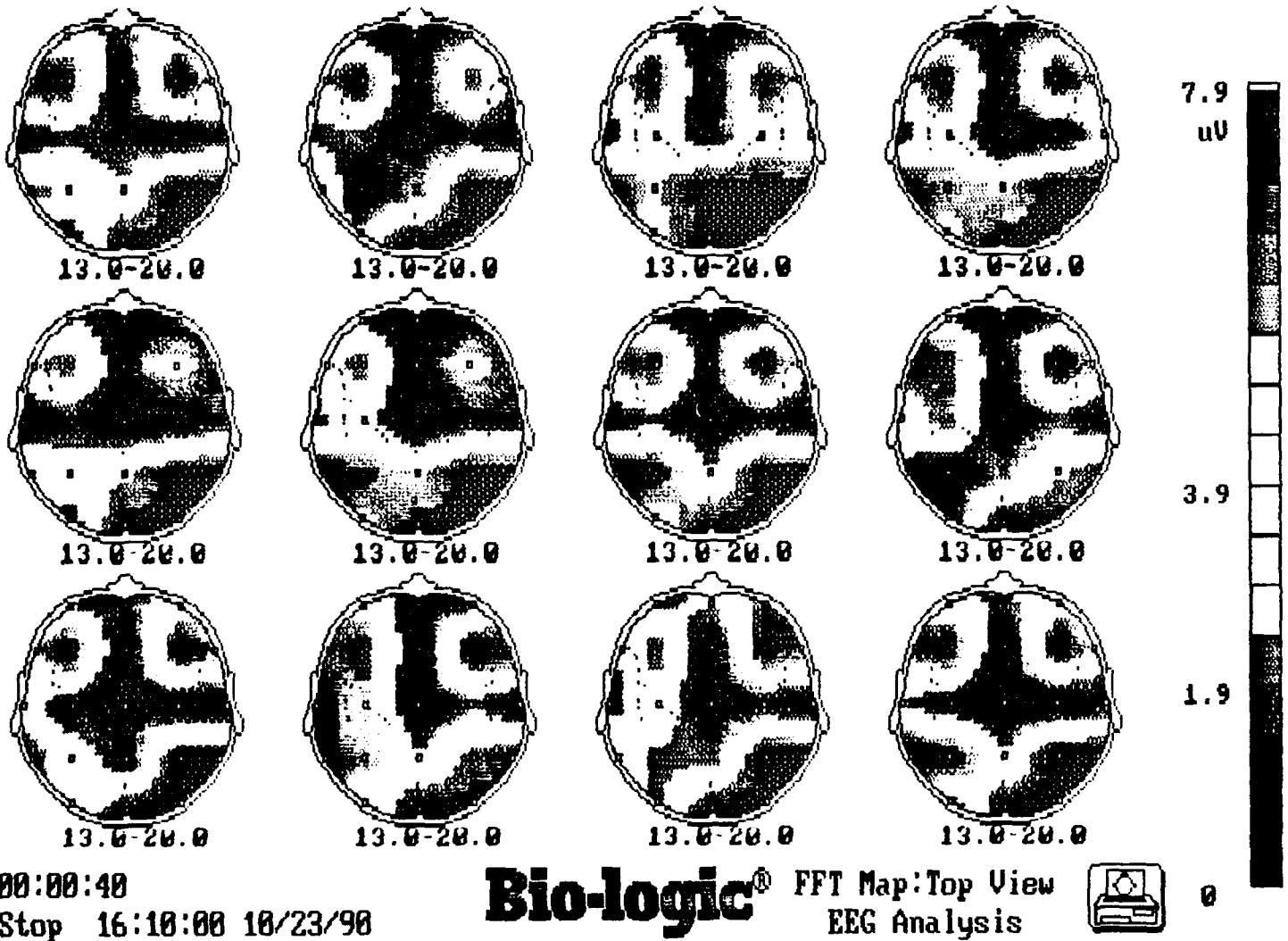Symptom Level 9-10

15.9
uV

7.9

3.9

00:02:38
Stop 13:45:32 10/24/90
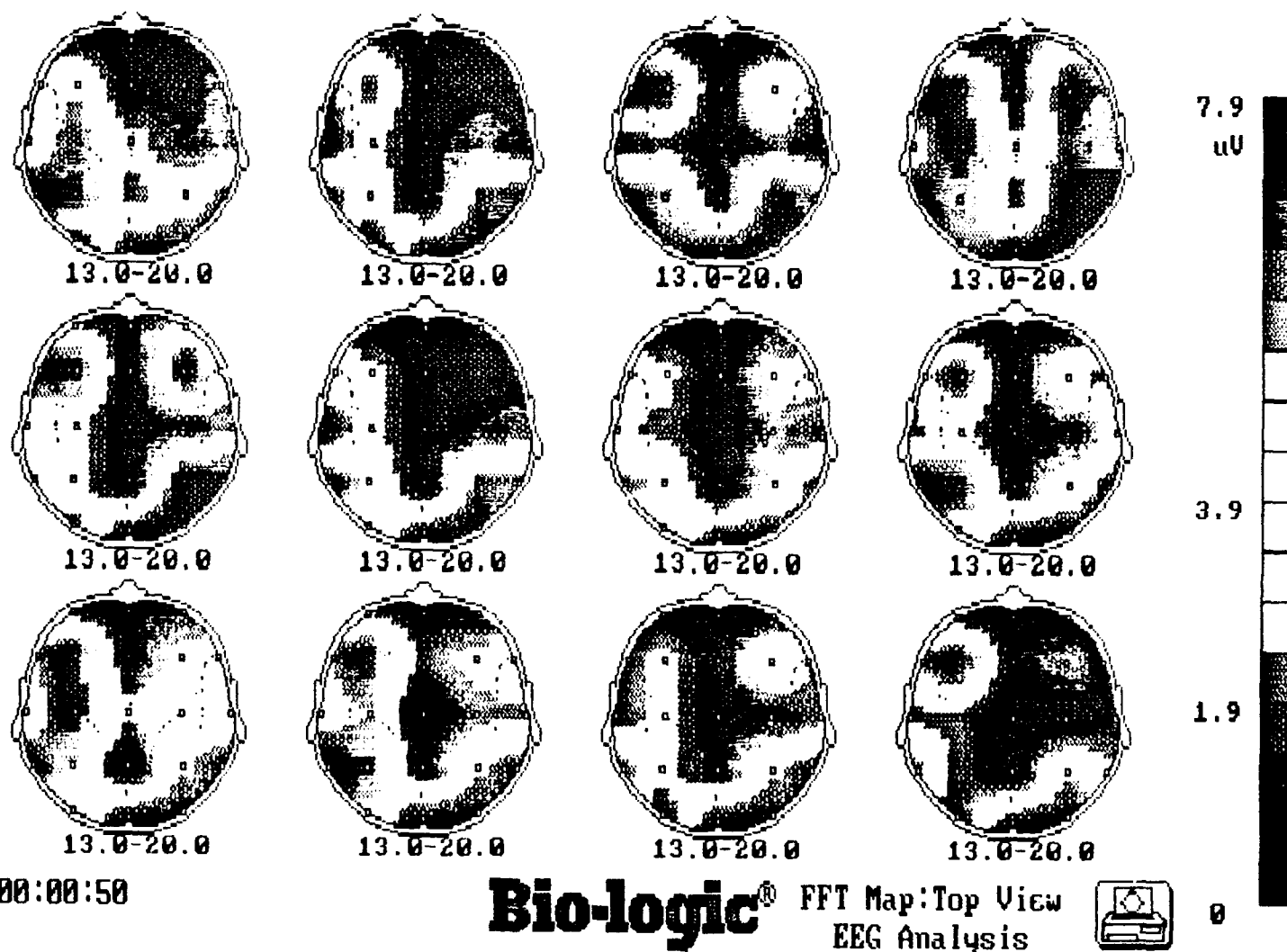
Bio-logic® FFT Map:Top View
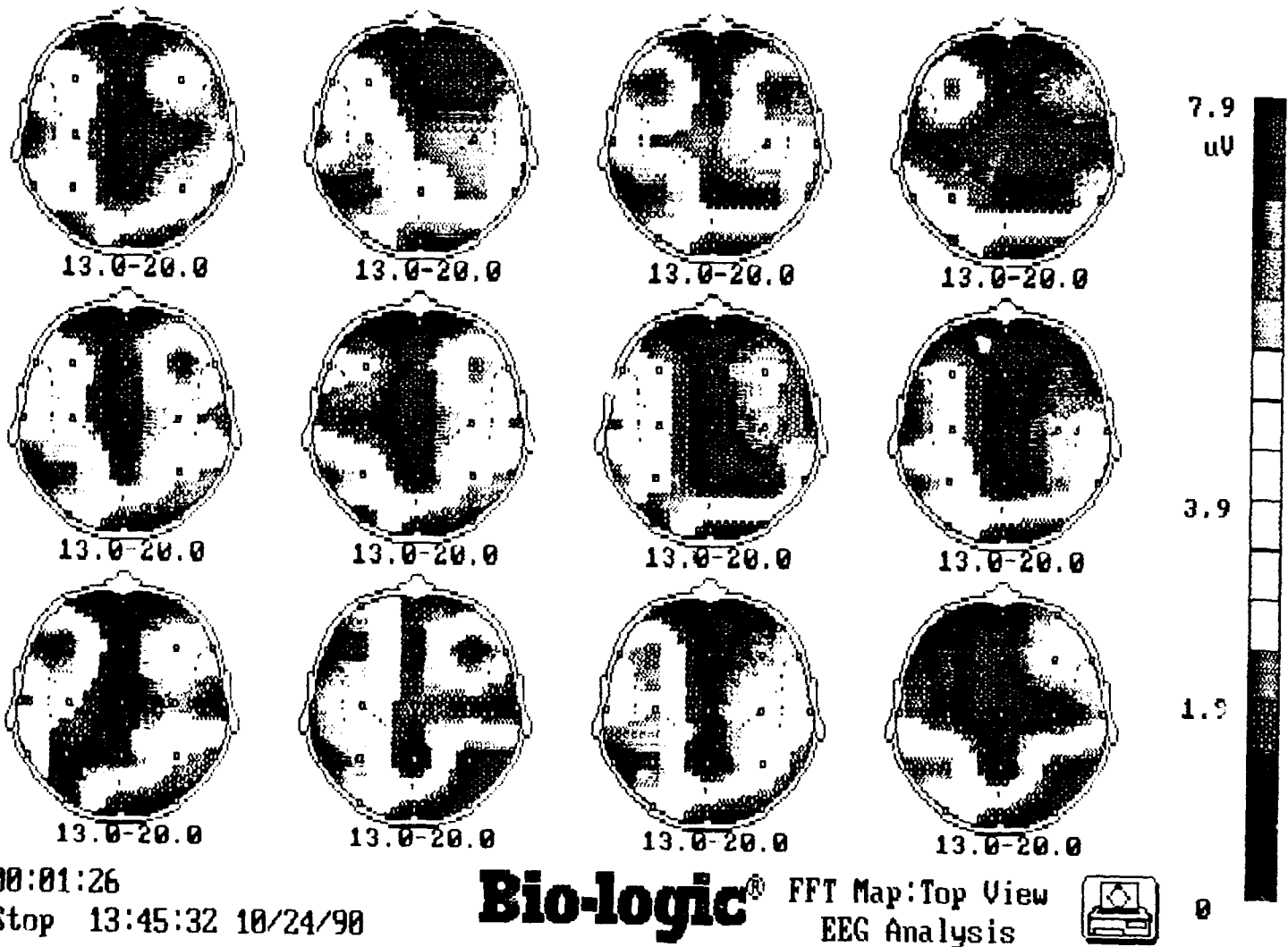EEG Analysis

0

Placebo Trial
Subject #8
Frequency 13.0 to 20.0 Hz
Baseline - Sitting at Rest

Placebo Trial
Subject #8
Frequency 13.0 to 20.0 Hz
Baseline – Spinning Prior to First HM

233

Placebo Trial
Subject #8
Frequency 13.0 to 20.0 Hz
Symptom Level 2-3

00:01:26
Stop 13:45:32 10/24/90

Bio-logic® FFT Map:Top View
EEG Analysis

7.9
uV

3.9

1.9

0

Placebo Trial
Subject #8
Frequency 13.0 to 20.0 Hz
Symptom Level 5

7.9
uV

3.9

1.9

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0

13.0-20.0   13.0-20.0   13.0-20.0   13.0-20.0
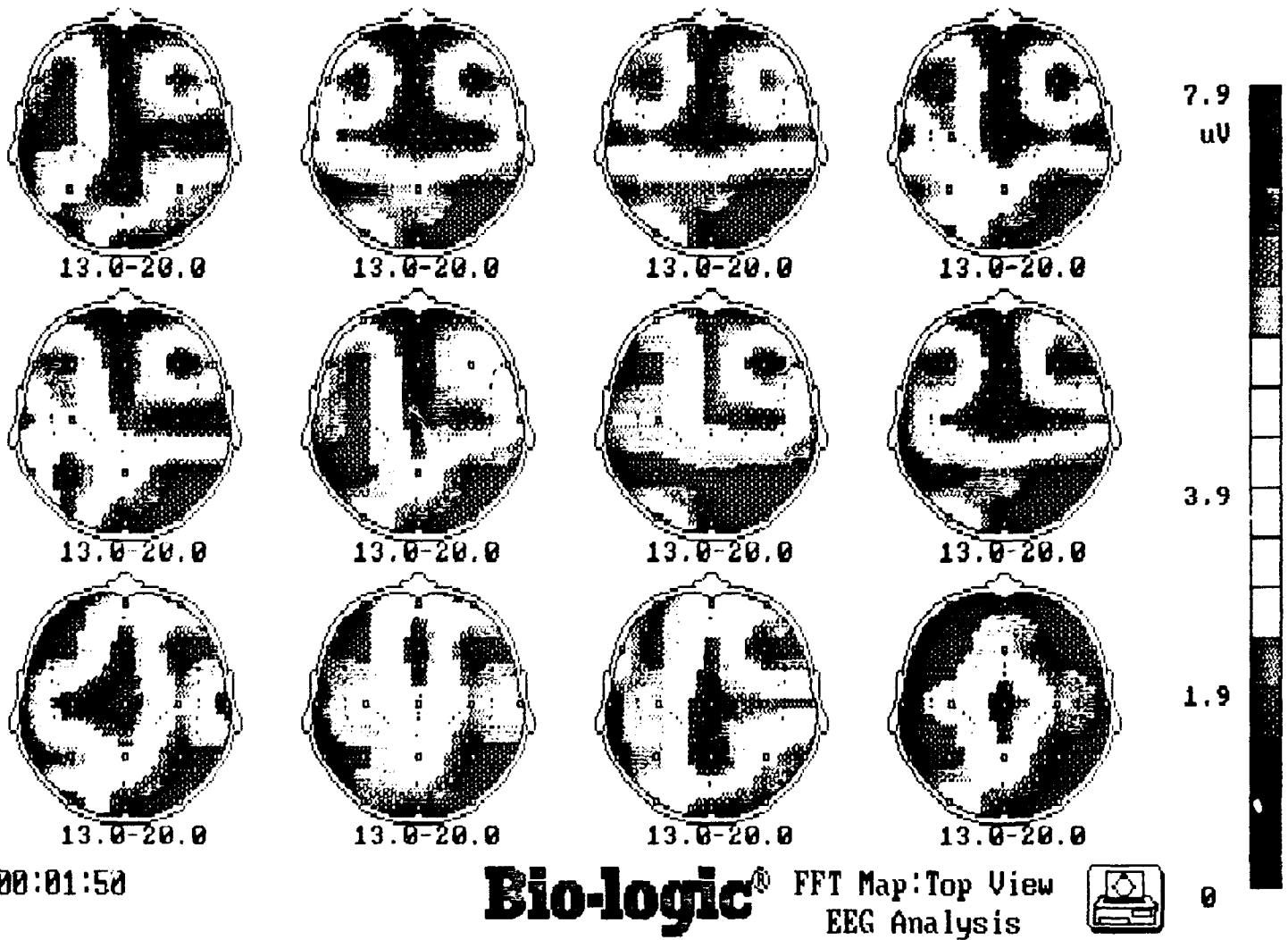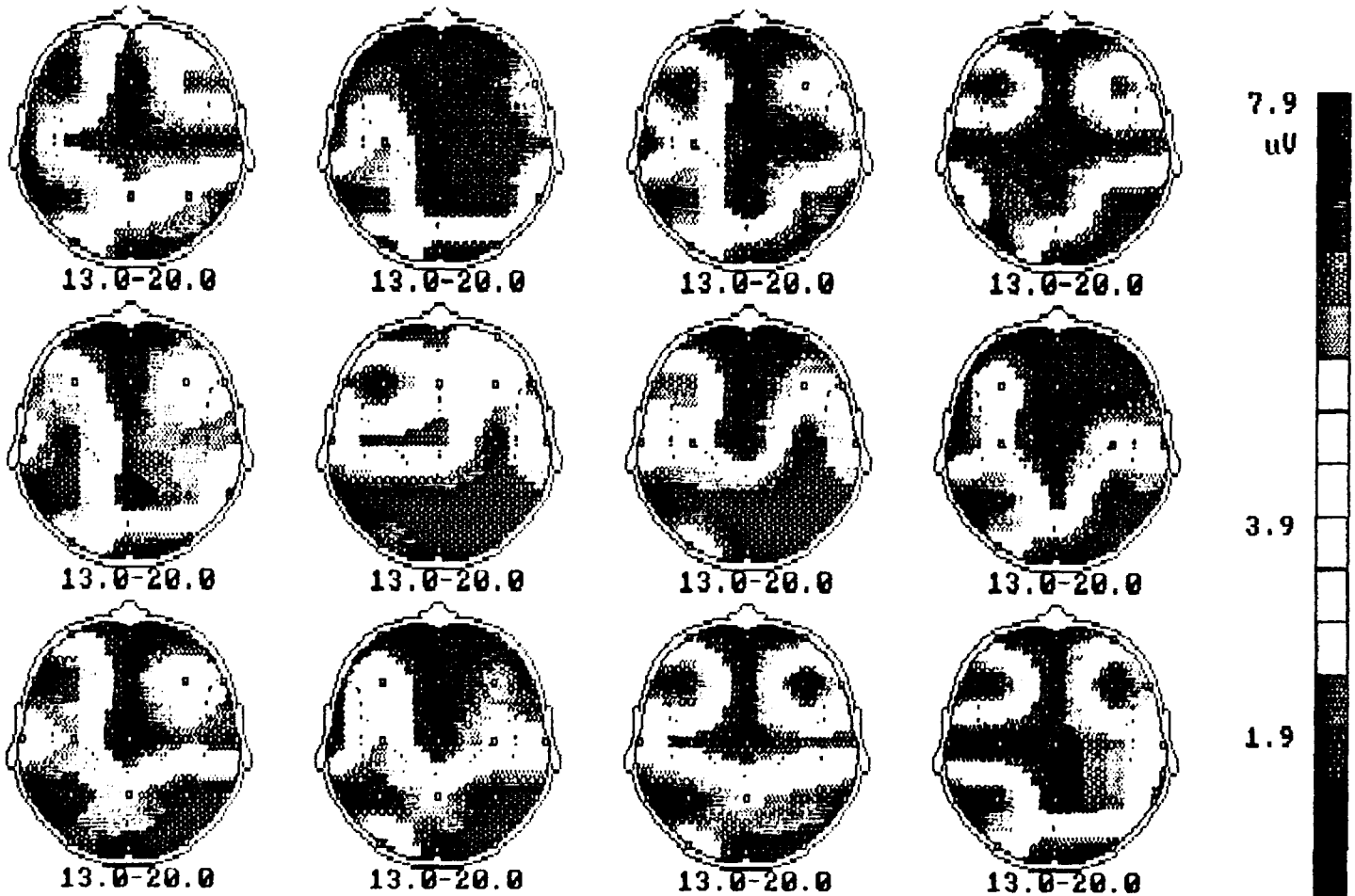
00:01:50   **Bio-logic®** FFT Map:Top View   0
EEG Analysis

235

Placebo Trial
Subject #8
Frequency 13.0 to 20.0 Hz
Symptom Level 7

Placebo Trial
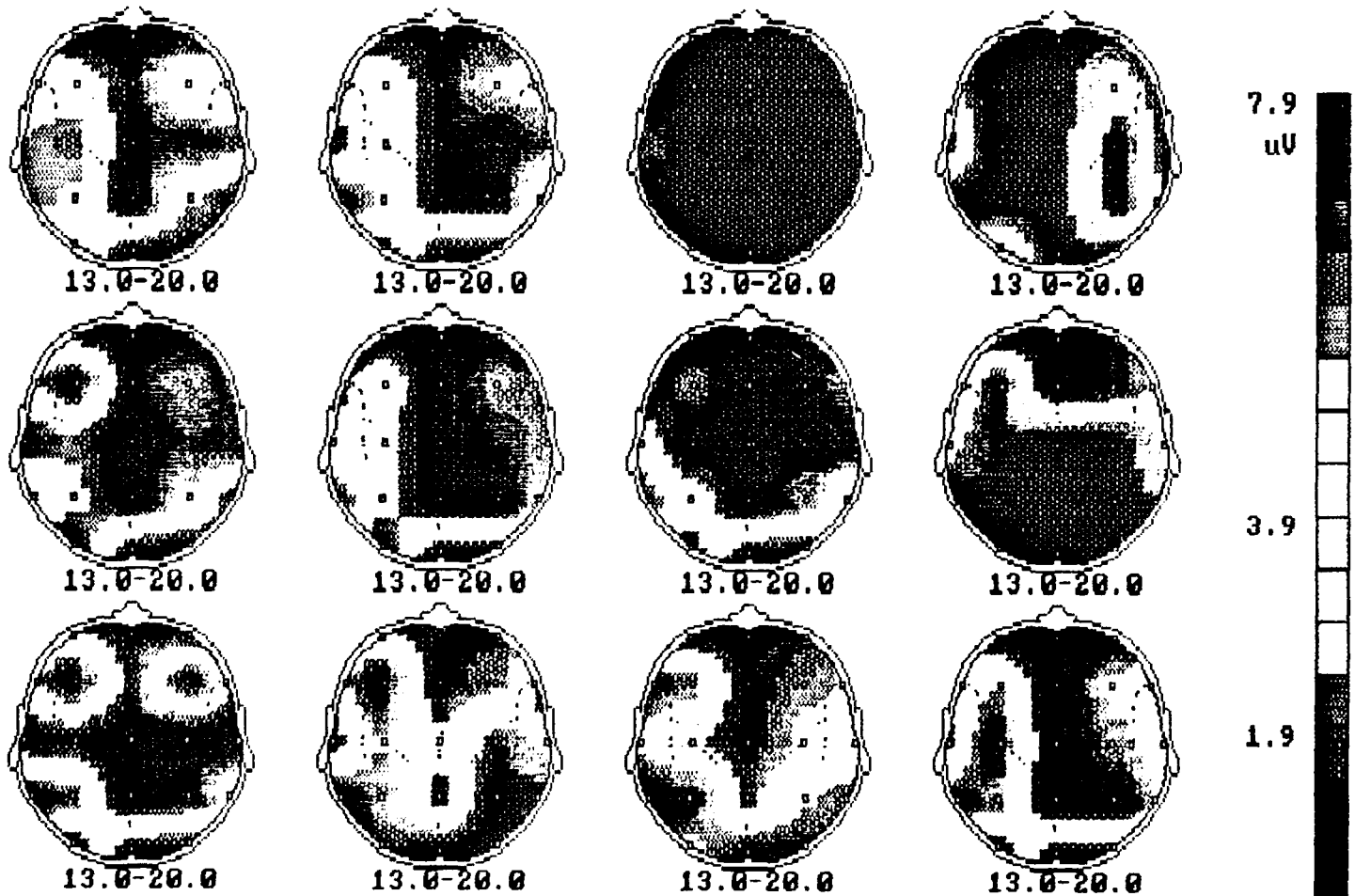Subject #8
Frequency 13.0 to 20.0 Hz
Symptom Level 9-10

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Vita

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE December 1990	3. REPORT TYPE AND DATES COVERED *Master's Thesis*

4. TITLE AND SUBTITLE

An Analysis of the Effects of Phenytoin in Treating Motion Sickness and the Effects of Motion Sickness on the Human Electroencephalogram

5. FUNDING NUMBERS

6. AUTHOR(S)

Todd Michael Banducci, Captain, USAF

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Air Force Institute of Technology, WPAFB OH 45433-6583

8. PERFORMING ORGANIZATION REPORT NUMBER

AFIT/GSO/ENG/90D-2

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

AAMRL/CC, WPAFB OH 45433-6543

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

This research had two goals: to continue the ongoing research at AFIT to determine the efficacy of the anticonvulsant drug phenytoin in combating the onset and progression of motion sickness; and to note whether or not there is a discernable similarity in the brains of the test subjects to indicate a common point of origin (epicenter) and propagation pattern of the effects of motion sickness in the brain. Eight male DoD personnel were used as subjects to complete twelve trials. Four subjects completed the phenytoin verses placebo double-blind crossover experiment. These four subjects experienced a 99% mean increase in their times-to-emesis and a 613% mean increase in their symptom-free-times, with one subject remaining asymptomatic throughout his phenytoin trial. Although some general tendencies were noted, no clearly evident point of origination or propagation pattern for motion sickness could be discerned in the brain.

14. SUBJECT TERMS

phenytoin, Dilantin, electroencephalogram, topographic brain mapping, motion sickness, space motion sickness, anticonvulsant, epilepsy

15. NUMBER OF PAGES

257

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT UL